

ANTICONVULSANT AGENTS UPDATE
FOCUS ON NEUROPATHIC PAIN
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MEDICAID DRUG USE REVIEW CRITERIA FOR OUTPATIENT USE

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Anticonvulsant agents are currently being prescribed for analgesia in neuropathic pain syndromes, in addition to the treatment of epilepsy.¹⁻⁴ Available anticonvulsants used in this manner include carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, pregabalin, topiramate, tiagabine, valproic acid, and zonisamide.

Neuropathic pain occurs in approximately 1% of the population. It is triggered by infection, trauma, metabolic abnormalities, chemotherapy, tumor infiltration, and inflammation. The pain may arise at a later time, often after the insult is removed. The severity of pain does not correlate with the extent of tissue damage.⁵ Diabetic peripheral neuropathy and postherpetic neuralgia are the two most common types of neuropathic pain. Anticonvulsants are considered to be among the adjunctive drugs of choice for neuropathic pain.^{4, 6-9} Pharmacologic therapy reduces pain but usually does not eliminate it or provide a cure. Anticonvulsant drugs have been used in pain management since the 1960s. Carbamazepine was one of the first anticonvulsants to demonstrate effectiveness in the management of trigeminal neuralgia.¹⁰⁻¹⁶ It is FDA-labeled to treat trigeminal neuralgia and is often prescribed as first-line therapy.¹⁷ Oxcarbazepine, gabapentin, lamotrigine and topiramate have also been studied for trigeminal neuralgia and may be useful alternatives to carbamazepine.¹⁸⁻²⁷ Gabapentin is an effective analgesic in both post-herpetic neuralgia,^{28, 29} and diabetic neuropathy,³⁰⁻³² although it is only labeled for postherpetic neuralgia. Pregabalin is the only anticonvulsant labeled for the treatment of both postherpetic neuralgia and diabetic peripheral neuropathy. Valproic acid and topiramate are approved for the prevention of migraine headaches. Phenytoin is not frequently used to treat neuropathic pain due to its narrow therapeutic range, adverse effects and lack of demonstrated efficacy. In general, anecdotal reports have suggested that most anticonvulsant medications have varying degrees of effectiveness in neuropathic pain syndromes.⁹ No head-to-head comparative trials between anticonvulsant agents exist. Additionally, the anticonvulsants are not effective for acute pain.^{9, 33} Table 1 summarizes the FDA-labeled indications for the available anticonvulsants.

The exact mechanism of action of the anticonvulsant agents in pain syndromes remains uncertain. Potential explanations include enhanced gamma-aminobutyric acid inhibition or a stabilization of the neuronal cell membranes or action via N-methyl-D-aspartate receptor sites. Carbamazepine, oxcarbazepine, lamotrigine and phenytoin act on voltage-gated sodium channels, while gabapentin and pregabalin act on voltage-gated calcium channels.⁵ Topiramate and tiagabine potentiate gamma-aminobutyric acid inhibition.³⁴ There is considerable variability in pain relief with the anticonvulsant agents. Some patients obtain relief with serum concentrations less than the therapeutic range in seizure disorders, whereas others require much higher dosing. Monitoring of serum drug concentrations is generally not necessary when dosing an anticonvulsant for pain or mood disorders.³⁵

Comparative efficacy between the agents is difficult to assess because there have been no head-to-head trials and pain relief is not consistently measured among the studies. Visual analog scales are commonly used to measure the patient's pain before and after treatment. In newer studies, study inclusion criteria require that patients have a visual analog score > 40 mm, indicating at least moderate pain (0= no pain and 100 = worst pain possible). The primary study outcome commonly used in pain studies is the percentage of patients with > 50% pain relief. This represents a clinically meaningful pain relief.³⁶

1. Indications for Use

Appendix A summarizes the published placebo-controlled or active controlled studies for the anticonvulsants in the treatment of diabetic peripheral neuropathy or postherpetic neuralgia.

Table 1. Labeled Indications for Use	
Drug	FDA-Labeled Indication
Carbamazepine	Partial seizures with complex symptoms, generalized tonic-clonic seizures, mixed seizure patterns or partial or generalized seizures. Trigeminal neuralgia
Gabapentin	Adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients > 12 years of age with epilepsy. Also indicated as adjunctive therapy for partial seizures in children 3 to 12 yrs of age. Post-herpetic neuralgia

Table 1. Labeled Indications for Use	
Drug	FDA-Labeled Indication
Lamotrigine	Adjunctive or monotherapy therapy in the treatment of partial seizures Adjunctive therapy in generalized seizures of Lennox-Gastaut syndrome Maintenance therapy of bipolar disorder
Levetiracetam	Adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy
Oxcarbazepine	Monotherapy or adjunctive therapy in the treatment of partial seizures in adults Adjunctive therapy in the treatment of partial seizures in children 4-16 yrs old
Pregabalin	Adjunctive therapy for adult patients with partial onset seizures Diabetic peripheral neuropathy Postherpetic neuralgia
Phenytoin	Control of grand mal and psychomotor seizures Prevent or treat seizures during or after neurosurgery
Tiagabine	Adjunctive therapy for the treatment of partial seizures
Topiramate	Adjunctive therapy was partial onset seizures, tonic clonic seizures or seizures associated with Lennox-Gastaut syndrome Monotherapy in partial onset or primary generalized tonic-clonic seizures Prophylaxis of migraine headaches
Valproic acid	Monotherapy or adjunctive therapy of various seizure types Mania with bipolar disorder Migraine headache prophylaxis
Zonisamide	Adjunctive therapy in the treatment of partial seizures

Diabetic Peripheral Neuropathy (DPN)

Treatment of DPN is based on disease modification including tight glycemic control and pain control.

The American Diabetes Association (ADA) recommends using tricyclic antidepressants as first line, followed by anticonvulsants, and then use of opioids or tramadol. If these treatments are not successful, patients should be referred to a pain clinic.³⁷ Tricyclic antidepressants should not be used in patients with cardiac conduction disease, long QT syndrome, myocardial infarction within 6 months, ventricular arrhythmias, or narrow angle glaucoma. Elderly patients are at increased risk of adverse effects from the tricyclic antidepressants.^{34, 38}

Pregabalin is the only anticonvulsant labeled for the treatment of DPN. It has been studied in 4 randomized double-blind, placebo-controlled trials involving a total of 1068 patients. The percent of patients with greater than a 50% decrease in pain scores from baseline ranged from 39% to 52%. In two of the clinical trials, patients were excluded if they had previously failed gabapentin 1200 mg/day or more. Doses greater than 300 mg/day do not confer significant additional benefit but do increase adverse reactions. Patients should be started on 150 mg/day and the dose may increased to 300 mg/day within one week.³⁹

Gabapentin has been studied in 2 randomized double-blind placebo controlled trials involving 205 patients.^{30, 40} The study by Gorson et al showed that gabapentin was not more effective than placebo at a dose of 900 mg/day. However, the washout period was inadequate in this study, pain scores did not return to baseline after crossover in patients who received gabapentin in the first phase. This may have underestimated the improvement with gabapentin. When gabapentin was titrated up to 3600 mg/day, it did reduce mean pain scores significantly more than placebo, $p < 0.001$. Data for the percentage of patients with a $> 50\%$ in pain score from baseline were not reported. Gabapentin has comparable efficacy to amitriptyline.^{32, 41} Gabapentin has been studied in combination with venlafaxine or morphine.^{42, 43} In these two small studies the combination therapy was more effective than gabapentin monotherapy. However, additional clinical trials are needed before this can be routinely recommended.

In all of the clinical trials with gabapentin and pregabalin, concomitant medications including antidepressants, narcotics and acetaminophen were allowed as long as the doses were stable. Pregabalin can be titrated to optimal dose in one week whereas gabapentin must be titrated over a 2 to 4 week period for the treatment of DPN.^{30, 39, 42, 43}

Topiramate has been studied for DPN in large scale clinical trials.^{36, 44} Study results have been conflicting. In a pooled analysis of 3 similar randomized, double-blind, placebo controlled trials involving 1269 patients, topiramate was no different than placebo. However, in a recent study of 323 patients with moderate to severe pain, topiramate 400 mg/day was superior to placebo. The

percent of patients with a 50% decrease in pain intensity score was 35.6% for topiramate and 21% with placebo, $p=0.005$.

Lamotrigine is also more effective than placebo for the treatment of DPN.⁴⁵ However, the slow dose titration and potential adverse reactions make this agent less desirable to use than other anticonvulsants.

Phenytoin has not consistently demonstrated efficacy for the management of DPN.^{46, 47} Additionally, hyperglycemia secondary to phenytoin is not desirable in the diabetic population.

Postherpetic Neuralgia (PHN)

The American Academy of Neurology guidelines recommend the use of tricyclic antidepressants, gabapentin, pregabalin, opioids and topical lidocaine patches for the treatment of PHN (categorized as medium to high efficacy, good strength of evidence and low level of side effects).⁴⁸ A meta-analysis by Hempenstall et al confirms these recommendations.⁴⁹

The only anticonvulsants adequately studied for postherpetic neuralgia are gabapentin and pregabalin. These agents are both FDA-labeled to treat PHN.^{39, 50}

No head-to-head comparative trials have been conducted with the anticonvulsants for the treatment of postherpetic neuralgia.

Gabapentin has been compared to placebo in two randomized controlled trials. Gabapentin 1800 mg/day reduced daily pain scores by approximately 34% from baseline. No additional benefit was observed with gabapentin doses greater than 1800 mg/day. The percent of patients with a > 50% decrease in baseline pain score was 32% and reported in only one study.^{28, 29} In both of these studies, patients were allowed to continue on antidepressants and narcotic medications, as long as the doses remained stable.

Pregabalin has also been compared to placebo in two randomized controlled trials. The percent of patients with a > 50% decrease in baseline pain score ranged from 26% to 50% with pregabalin compared with 10% to 20% with placebo, $p<0.001$.^{51, 52}

In all of the clinical trials with gabapentin and pregabalin, concomitant medications including antidepressants, narcotics and acetaminophen were allowed as long as the doses were stable.

An open-label study in 24 patients with PHN showed that 84% of patients who failed gabapentin and carbamazepine therapy responded to oxcarbazepine 900 mg/day. However, the gabapentin doses ranged from 900 -1200 mg/day, and a significant argument can be made that patients were underdosed.⁵³

Trigeminal Neuralgia

Carbamazepine is the best studied anticonvulsant for the management of chronic pain due to trigeminal neuralgia.

Gabapentin and pregabalin have not been studied for trigeminal neuralgia in randomized controlled trials and topiramate has not demonstrated efficacy over placebo.²⁰

Carbamazepine has been evaluated in 3 randomized, double-blind, placebo-controlled trials and in 3 randomized, double-blind, active control studies.^{10, 16, 54-57} Efficacy was expressed differently in all the trials. Rockliff et al showed that carbamazepine 200 mg three times per day for three days produced satisfactory pain control in 16 out of 20 patients.¹⁰ Nicol et al showed that 27 out of 37 patients had an excellent or good response after 14 days of carbamazepine therapy.¹⁶ Campbell et al found that carbamazepine 400 mg to 800 mg/day reduced pain intensity 58% compared with 26% of patients receiving placebo.⁵⁷ Carbamazepine provides similar pain relief as tocainide, is more effective than tizanidine, and is less than pimozone.⁵⁴⁻⁵⁶

Lamotrigine has been studied in trigeminal neuralgia in one placebo-controlled cross-over study.²⁵ Fourteen patients were titrated on lamotrigine 50 mg/day up to 400 mg/day for 14 days. However, these patients were also on carbamazepine and/or phenytoin. Lamotrigine provided better pain relief than placebo, $p=0.001$. In an open-label cross over study of 18 patients with trigeminal neuralgia and multiple sclerosis, lamotrigine 400 mg/day provided greater pain relief than carbamazepine 400 to 800 mg/day, $p=0.0003$.⁵⁸

The off-label uses for the anticonvulsants specific to pain syndromes are summarized in Table 2. Trials were graded for quality according to the US Preventative Services Task Force Guidelines for Rating Quality of Evidence.⁵⁹ These guidelines are summarized in Table 3.

Table 2. Unlabeled Uses of the Anticonvulsants		
Drug	Unlabeled Uses for Pain and Movement	Highest Level of Evidence for Unlabeled Uses
Carbamazepine	Peripheral neuropathic pain ^{6, 60-64}	I
	Restless legs syndrome ^{65, 66}	I
	Phantom limb pain ⁶⁷	III
	Hereditary and nonhereditary chorea ⁶⁸⁻⁷⁰	II.1
Gabapentin	Diabetic neuropathy ^{29, 30 71 72, 73}	I
	Peripheral neuropathy ⁷⁴⁻⁷⁷	III
	Trigeminal neuralgia ^{73, 78}	II.3
	Migraine prophylaxis ⁷⁹	I.1
	Central pain ^{73, 80, 81}	III
	Neuropathic cancer pain ⁷³	III
	HIV polyneuropathy ⁷³	III
	Multiple Sclerosis ⁸²	I.1
Lamotrigine	Neuropathic pain ^{45, 83, 84}	I
	HIV-associated polyneuropathy ⁸³	I.1
	Trigeminal neuralgia ^{18, 21, 24, 25}	I
	Central poststroke pain ⁸⁵	I.1
	Phantom limb pain ⁸⁶	III
Levetiracetam	Cancer pain ⁸⁷	III
	Migraine headache ^{88, 89}	III
	Neuropathic pain ⁹⁰	III
	Postherpetic neuralgia ⁹¹	III
	Spasticity ⁹²	III
Oxcarbazepine	Trigeminal neuralgia ^{19, 22, 26, 93}	II.3
	Neuropathic pain ^{94, 95}	II.3
	Post-herpetic neuralgia ^{53, 96}	II.3
Pregabalin	Generalized anxiety disorder ⁹⁷⁻¹⁰¹	I
	Social anxiety disorder ¹⁰²	I.1
	Fibromyalgia ¹⁰³	I.1
Phenytoin	Diabetic neuropathy ^{46, 47, 104}	Evidence not conclusive to support use
	Adjuvant therapy for cancer pain ^{105, 106}	I.1
	Chronic pain ¹⁰⁷⁻¹⁰⁹	III
	Adjunctive therapy for mania ¹¹⁰	I.1
	Peripheral neuropathic pain ¹¹¹	I.1
	Second line for trigeminal neuralgia ^{112, 113}	III
Tiagabine	Sensory neuropathy ¹¹⁴	II.3
	Chronic pain ¹¹⁵	II.3
	Spasticity ¹¹⁶	III
Topiramate	Diabetic neuropathy ^{36, 44, 117}	I – mixed results, data not conclusive
	Trigeminal neuralgia ^{20, 24, 27}	I
	Binge Eating Disorder ¹¹⁸	I.1
	Cluster headaches ¹¹⁹⁻¹²⁴	III
	Phantom limb pain ¹²⁵	III
	Spinal cord injury pain ¹²⁶	III
Valproic acid	Trigeminal neuralgia ^{127, 128}	II.3
	Alcohol Withdrawal ^{129, 130}	I

Table 2. Unlabeled Uses of the Anticonvulsants		
Drug	Unlabeled Uses for Pain and Movement	Highest Level of Evidence for Unlabeled Uses
	Cancer-related neuropathic pain ¹³¹	I.1
	Diabetic neuropathy ¹³²	I.1
	Post-traumatic stress disorder ^{133, 134}	II.2
	Cluster headaches ^{135, 136}	II.2
	Chronic Daily Headache ¹³⁷⁻¹³⁹	II.2
	Panic Disorder ^{140, 141}	III
	Sydenham's chorea ⁶⁸	II.1
	Schizoaffective disorders ¹⁴²	III
Zonisamide	Diabetic peripheral neuropathy ¹⁴³	I.1 – not more effective than placebo
	Central post-stroke pain ¹⁴⁴	III
	Refractory migraine ¹⁴⁵	III
	Bipolar disorder ^{146, 147}	III

Table 3. Guidelines for Grading Quality of Evidence

I.	Evidence from more than one properly randomized controlled trial
I.1	Evidence from one properly randomized controlled trial
II.1	Evidence from well-designed controlled trial without randomization
II.2	Evidence from well-designed cohort or case-controlled analytic studies
II.3	Evidence obtained from multiple time series with or without intervention. Dramatic results in uncontrolled experiments
III.	Descriptive studies or case reports, opinions of respected authorities based on clinical evidence, or reports of expert committees.

Adapted from Reference⁵⁹

2. Maximum usual dosage and Cost

Usual and maximum adult doses for FDA-labeled indications are listed in **Table 4**. Usual doses for unlabeled uses are listed in **Table 5**. Monthly costs are shown in **Table 6**.

Table 4. Usual Adult Doses for the FDA-Labeled Indications of the Anticonvulsants			
Drug	Dosage Form(s)	Usual Adult Dose from Product Labeling	Maximal Recommended Dose per Product Labeling*
Carbamazepine (Tegretol®, Tegretol XR, Carbatrol®, Epitol®, Atretol®)	Chewable tablets: 100 mg, 200 mg Tablets: 200 mg Tablets, extended release 100 mg, 200 mg, 400 mg Capsules, extended release 200 mg, 300 mg Suspension 100 mg/5 mL	Epilepsy Start: 200 mg BID Maintenance: 800 – 1200 mg/day	Usual maximum is 1200 mg/day. Rarely patients may need up to 1600 mg/day.
		Trigeminal neuralgia Start: 100 mg BID Maintenance: 400 – 800 mg/day.	1200 mg/day
Gabapentin (Neurontin®)	Capsules: 100 mg, 300 mg, 400 mg Tablets: 600 mg, 800 mg Solution: 250 mg/5mL	Epilepsy Start: 300 mg TID Maintenance: 900 – 1800 mg/day	3600 mg/day
		Post-herpetic Neuralgia Start Day 1: 300 mg; Day 2: 300 mg bid; Day 3: 300 mg tid and continue. Maintenance 900 – 1800 mg/day	3600 mg/day No additional benefit seen over 1800 mg/day.
Lamotrigine (Lamictal®)	Tablets: 25 mg, 100 mg, 150 mg, 200 mg Chewable tablets: 2 mg, 5 mg	Epilepsy <i>Added to AED regimen containing valproic acid:</i>	<i>Added to AED regimen containing valproic acid: 200 mg/day</i>

Table 4. Usual Adult Doses for the FDA-Labeled Indications of the Anticonvulsants			
Drug	Dosage Form(s)	Usual Adult Dose from Product Labeling	Maximal Recommended Dose per Product Labeling*
	and 25 mg	<p>Week 1 and 2: 25 mg QOD. Week 3 and 4: 25 mg QD Maintenance: 100 – 200 mg/day. <i>Added to AED regimen without valproic acid:</i> Week 1 and 2: 50 mg/day Week 3 and 4: 50 mg BID Maintenance: 300 – 500 mg/day Bipolar disorder <i>For patients not on carbamazepine, phenytoin, phenobarbital, primidone, rifampin or valproate:</i> Weeks 1 and 2: 25 mg/day Weeks 3 and 4: 50 mg/day Week 5: 100 mg/day Week 6 200 mg/day Maintenance: 200 mg/day. <i>For patients on valproate</i> Weeks 1 and 2: 25 mg every other day Weeks 3 and 4: 25 mg/day Week 5: 50 mg/day Week 6 100 mg/day Maintenance: 100 mg/day. <i>For patients taking carbamazepine, phenytoin, phenobarbital, primidone, rifampin</i> Weeks 1 and 2: 50 mg/day Weeks 3 and 4: 100 mg/day Week 5: 200 mg/day Week 6 300 mg/day Maintenance: up to 400 mg/day.</p>	<p><i>Added to AED regimen without valproic acid:</i> 500 mg/day usual max. Doses up to 700 mg/day have been used.</p> <p>Maximum dose is 200mg/day for patients not on other AEDs. No additional benefit seen with 400 mg/day.</p> <p>For patients on valproate, maximum dose is 100 mg/day.</p> <p><i>For patients on carbamazepine, phenytoin, phenobarbital, primidone, rifampin and not valproate, maximum dose is 400 mg/day.</i></p>
Levetiracetam (Keppra®)	Tablets: 250 mg, 500 mg, 750 mg	<p>Epilepsy Start 500 mg BID Maintenance: 1000 – 3000 mg/day</p>	<p>3000 mg/day No evidence that doses greater than 3000 mg/day confer additional efficacy.</p>
Oxcarbazepine (Trileptal®)	Tablets: 150 mg, 300 mg, 600 mg	<p>Epilepsy <i>Added to existing AEDs</i> Start 300 mg BID Maintenance 1200 mg/day <i>Monotherapy</i> 1200 – 2400 mg/day given as BID regimen.</p>	<p><i>Added to existing AEDs</i> 1200 mg/day. Doses up to 2400 mg/day have been used but many patients cannot tolerate side effects. <i>Monotherapy</i> 2400 mg/day</p>
Pregabalin (Lyrica®)	Capsules: 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg	<p>Epilepsy, partial onset seizures Start 150 mg/day divided either BID or TID. Postherpetic neuralgia Start 150 mg/day divided either BID or TID.</p>	<p>For postherpetic neuralgia and diabetic neuropathy 300 mg/day</p> <p>Epilepsy 600 mg/day</p>

Table 4. Usual Adult Doses for the FDA-Labeled Indications of the Anticonvulsants			
Drug	Dosage Form(s)	Usual Adult Dose from Product Labeling	Maximal Recommended Dose per Product Labeling*
		Diabetic peripheral neuropathy Start 150 mg/day divided TID.	
Phenytoin (Dilantin®)	Chew tabs 50 mg, Suspension 125 mg/5mL Capsules 100 mg Extended release capsules 30 mg, 100 mg	Epilepsy Start 100 mg TID Maintenance 300 - 600 mg/day	Serum concentrations 10 – 20 mcg/mL. Dosing is a balance of optimal control of symptoms without signs of clinical toxicity
Tiagabine (Gabitril®)	Tablets: 4 mg, 12 mg, 16 mg, 20 mg	Epilepsy Start 4 mg QD. Increase by 4 mg per week. Maintenance 32 - 56 mg/day in 2 – 4 divided doses.	56 mg/day
	Tablets 25 mg, 100 mg, 200 mg Capsules: 15 mg, 25 mg	Epilepsy Start 25 to 50 mg/day and increase by 25 to 50 mg per week. Maintenance 200 mg BID Migraine Headache Start at 25 mg/day and increase weekly by 25 mg to dose of 50 mg BID.	1600 mg/day Doses above 400 mg/day have not been shown to improve response in adults with partial onset seizures.

Table 4. Usual Adult Doses for the FDA-Labeled Indications of the Anticonvulsants			
Drug	Dosage Form(s)	Usual Adult Dose from Product Labeling	Maximal Recommended Dose per Product Labeling*
Topiramate (Topamax®)			
Valproic acid (Depakene®, Depakote®, Depacon®, Depakote ER®)	Capsules 250 mg Syrup 250 mg/5mL, Delayed release tablets 125 mg, 250 mg, 500 mg Extended release tablets 500 mg Capsules 125 mg	Epilepsy Start 10 – 15 mg/kg/day. Increase by 5 to 10 mg/kg/week to achieve desired response.	60 mg/kg/day Therapeutic concentration 50 to 100 mcg/mL.
		Migraine prophylaxis Start 250 mg BID Maintenance 500 – 1000 mg/day. <i>Depakote ER</i> Start 500 mg QD Maintenance 500 – 1000mg/day	1000 mg/day
		Mania Start 750 mg/day in divided doses. Doses should be increased to achieve clinical effect.	60 mg/kg/day Therapeutic plasma concentrations 50 –125 mcg/mL.
Zonisamide (Zonegran®)	Capsules 100 mg	Epilepsy Start 100 mg QD Maintenance 100 – 600 mg/day	600 mg/day In clinical trials, doses greater than 400 mg/day did not confer additional efficacy.

Abbreviations: AEDs= antiepileptic drugs; BID = twice daily; TID= three times daily; QD= once daily.

*Note: Occasionally doses greater than the maximal dose listed in the product labeling are needed to control a patient's symptoms. These judgments should be made on a case by case basis.

Table 5. Usual Dosage for the Anticonvulsants for Unlabeled Uses

Drug	Unlabeled Use	Usual Adult Dose from Published Literature
Carbamazepine	Peripheral neuropathic pain ^{6, 60-64}	600 mg/day
	Restless legs syndrome ^{65, 66}	300 – 600 mg/day (2 patients benefited from increasing dose to 1000 mg/day)
	Phantom limb pain ⁶⁷	600 – 1400 mg/day (goal therapeutic blood level 8 – 12 mcg/mL)
	Hereditary and nonhereditary chorea ⁶⁸⁻⁷⁰	All studies in children. Doses ranged from 15 to 20 mg/kg/day.

Drug	Unlabeled Use	Usual Adult Dose from Published Literature
Gabapentin	Diabetic neuropathy ^{29, 30 71 72, 73}	900 – 3600 mg/day
	Peripheral neuropathy ^{71, 74-77}	900 – 3600 mg/day
	Trigeminal neuralgia ^{73, 78}	600 – 2400 mg/day
	Migraine prophylaxis ^{79, 148}	1200 mg/day fixed dose used in 1 study; other study titrated from 900 – 2400 mg/day. Both studies showed decreased frequency of migraine.
	Central pain ^{73, 80, 81}	900 – 2400 mg/day
	Neuropathic cancer pain ⁷³	900 – 2400 mg/day
	HIV polyneuropathy ^{73, 149}	900 – 2400 mg/day
	Multiple Sclerosis ⁸²	900 – 2700 mg/day. Spasticity may respond better to higher doses of gabapentin.
Lamotrigine	Neuropathic pain ^{45, 83, 84}	25 – 400 mg/day
	HIV-associated polyneuropathy ⁸³	25 – 300 mg/day
	Trigeminal neuralgia ^{18, 21, 24, 25}	400 mg/day (optimal maintenance dose)
	Central poststroke pain ⁸⁵	200 mg/day (dose started at 25 mg/day and titrated up to optimal dose of 200 mg/day)
	Phantom limb pain ⁸⁶	50 – 200 mg/day
Levetiracetam	Autism ¹⁵⁰	Only studied in children ages 4-10. Dose started at 13 mg/kg/day and increase to maximum of 54 mg/kg/day not exceeding 3 g.
	Mania ¹⁵¹	2500 mg/day
Oxcarbazepine	Bipolar disorder ¹⁵²⁻¹⁵⁵	900 – 2100 mg/day
	Notalgia paresthetica ¹⁵⁶	600 – 1200 mg/day
	Trigeminal neuralgia ^{19, 22, 26, 93}	600 – 1200 mg/day (some patients have required up to 2400 mg/day).
Phenytoin	Diabetic neuropathy ^{46, 47, 104}	300 mg/day
	Adjuvant therapy for cancer pain ^{105, 106}	200 mg/day
	Chronic pain ¹⁰⁷⁻¹⁰⁹	IV bolus doses of 500 mg help with immediate pain control.
	Adjunctive therapy for mania ¹¹⁰	400 – 500 mg/day (mean phenytoin blood levels at week 5 were 21.4 mcg/mL in 15 patients) ⁶²
	Peripheral neuropathic pain ^{111, 112, 113}	15 mg/kg IV over 2 hrs effective for acute flare-ups of neuropathic pain.
	Second line for trigeminal neuralgia ^{112, 113}	300 – 400 mg/day
Pregabalin	Fibromyalgia ¹⁰³	450 mg/day (doses of 150 – 300 mg/day were not more effective than placebo).
	Generalized anxiety disorder ^{97, 100, 101}	150 – 600 mg/day
	Social anxiety disorder ⁹⁸	150 – 600 mg/day
Tiagabine	Sensory neuropathy ¹¹⁴	4 - 16 mg/day (8 mg/day was most effective dose in this study) ¹¹⁴
	Spasticity ¹¹⁶	Studied in children at dose of 0.2 – 1.1 mg/kg/day
	Anxiety ¹⁵⁷	Dose titrated to 8 mg BID
Topiramate	Cluster headaches ¹¹⁹⁻¹²⁴	25 – 200 mg/day
	Migraine prophylaxis ^{122, 123, 158}	25 – 200 mg/day
	Bipolar disorder ¹⁵⁹⁻¹⁶¹	100 – 300 mg/day (doses started at 25 mg and titrated to goal). Some patients have required up to 1300

Drug	Unlabeled Use	Usual Adult Dose from Published Literature
	Trigeminal neuralgia ^{20, 24, 27}	200 – 300 mg/day
	Binge Eating Disorder ¹¹⁸	50 – 600 mg/day (median dose 200 mg/day)
Valproic acid	Trigeminal neuralgia ^{127, 128}	600 – 1200 mg/day
	Alcohol Withdrawal ^{129, 130}	1000 to 1200 mg/day for 4 – 7 days
	Diabetic neuropathy ¹³²	1200 mg/day
	Cancer-related neuropathic pain ¹³¹	400 – 1200 mg/day (Studies were European and so doses do not correspond to dosage forms available in USA)
	Post-traumatic stress disorder ^{133, 134}	250 – 2000 mg/day
	Cluster headaches ^{135, 136}	500 – 2000 mg/day
	Chronic Daily Headache ¹³⁷⁻¹³⁹	500 – 2000 mg/day
Zonisamide	Bipolar disorder ^{146, 147}	100 – 600 mg/day
	Weight loss ¹⁶²	100 – 600 mg/day

Abbreviations: AEDs= antiepileptic drugs; BID = twice daily; TID= three times daily; QD= once daily.

Table 6. Usual Monthly Costs.

Drug	Dosage Form(s)	Dose Example	Monthly Cost #
Carbamazepine	Tablets: 200 mg	200 mg tid	90 = *
Tegretol®,	Tablets: 200 mg	200 mg tid	90=
Gabapentin (Neurontin®)	Capsules: 300 mg Capsules: 600 mg	300 mg tid 600 mg tid	90 = 90 =
Lamotrigine (Lamictal®)	Tablets: 150 mg	150 mg bid	60 =
Levetiracetam (Keppra®)	Tablets: 500 mg	1000 mg bid	120 (500mg) =
Oxcarbazepine (Trileptal®)	Tablets: 600 mg	600 mg bid	60 = \$
Phenytoin (Dilantin®)	Capsules 100 mg	200 mg bid	120 (100mg) = \$
	Capsules 100 mg	200 mg bid	120 (100mg) = \$
Pregabalin (Lyrica®)	Capsules 100 mg	100 mg tid	90 = \$
Tiagabine (Gabitril®)	Tablets: 16 mg	16 mg tid	90 = \$
Topiramate (Topamax®)	Tablets 200 mg	600 mg bid	180 (200mg) = \$
Valproic acid (Depakene®,	Capsules 250 mg	500 mg bid	120 (200mg) = \$*
	Capsules 250 mg	500 mg bid	120 (200mg) = \$*
Zonisamide (Zonegran®)	Capsules 100 mg	200 mg bid	120 (100mg) = \$

Costs are based on the Medicaid EAC (Estimated Acquisition Cost). Costs are for drug only and do not include dispensing fees.

* M indicates MAC, or Maximum Allowable Cost.

3. **Duration of therapy**

Patients with pain syndromes may require indefinite therapy. Efficacy and safety should be reviewed periodically with long-term use. Patients should be maintained on the lowest effective dose to control symptoms. Abrupt withdrawal of any of the AEDs should be avoided. Each product should be tapered according to the product labeling.

4. **Duplicative therapy**

For neuropathic pain syndromes, anticonvulsants and analgesics are duplicative therapy. However, combination therapy may be indicated upon failure of a reasonable trial of monotherapy with an anticonvulsant or analgesic medication. In many of the clinical trials, patients were allowed to continue aspirin, NSAIDs, acetaminophen, opioids, and antidepressants. Use of more than one anticonvulsant for the treatment of neuropathic pain is not indicated. In open-label, uncontrolled trials multiple anticonvulsants have been used to treat neuropathic pain. However, due to the potential for adverse reactions and drug interactions, lack of controlled clinical trials, and high-cost, therapy should be maximized with a single anticonvulsant agent.

5. **Drug-drug interactions** ^{163-165, 166}

Unlike most anticonvulsants, gabapentin and pregabalin are not associated with significant drug interactions.

Acetaminophen (Minimal)

Carbamazepine may increase the risk of acetaminophen hepatotoxicity. At usual therapeutic oral doses of carbamazepine and acetaminophen, no special monitoring is required. Phenytoin can increase metabolism of acetaminophen resulting in decreased acetaminophen effectiveness. Concurrent lamotrigine and acetaminophen may decrease plasma levels of lamotrigine and increase urinary excretion.

Acetazolamide (Moderate)

Topiramate inhibits some isoenzymes of carbonic anhydrase. The combined effect of acetazolamide and topiramate increases the risk of kidney stones. Concomitant use should be avoided. Concurrent use of acetazolamide and zonisamide predisposes patients to heat stroke.

Acetylcysteine (Moderate)

Increases risk of subtherapeutic carbamazepine levels. Closely monitor carbamazepine levels in patients also receiving N-acetylcysteine.

Alprazolam (Moderate)

Concurrent use of carbamazepine and alprazolam may require higher doses of alprazolam. The dose of alprazolam should be decreased if carbamazepine is discontinued.

Allopurinol (Moderate)

Concurrent use of phenytoin and allopurinol may result in increased phenytoin levels.

Amiodarone (Moderate)

Concurrent amiodarone and phenytoin therapy results in increased phenytoin serum levels.

Amitriptyline, Desipramine, Doxepin, Nortriptyline, Protriptyline, Trimipramine (Minimal)

Carbamazepine may decrease tricyclic antidepressant effectiveness. Serum levels of both agents should be considered when either agent is added or discontinued, with appropriate dosage adjustments made accordingly. Phenytoin may induce the metabolism of tricyclic antidepressants resulting in decreased effectiveness. Concurrent valproic acid and tricyclic antidepressants can alter the pharmacokinetics of either agent.

Amprenavir (Moderate)

Carbamazepine reduces amprenavir efficacy and amprenavir increases carbamazepine concentrations. Concurrent amprenavir and phenytoin may result in reduced amprenavir concentrations.

Anisindione, Warfarin (Moderate)

Decreased anticoagulant effectiveness, the prothrombin time ratio or INR should be closely monitored with the addition and withdrawal of treatment with carbamazepine or phenytoin.

Aspirin (Moderate)

Concurrent valproic acid and aspirin may lead to increased free valproic acid serum levels and increased half-life. Monitor for valproic acid toxicity.

Antacids (Minimal)

Separate administration of antacids and gabapentin or phenytoin by 2 hours. Antacids reduce both gabapentin and phenytoin bioavailability. Concurrent valproic acid and antacids increase the bioavailability of valproic acid.

Atorvastatin, simvastatin (Minimal)

Phenytoin may induce metabolism of some HMG-CoA reductase inhibitors resulting in decreased efficacy.

Azithromycin (Moderate)

Concurrent azithromycin and phenytoin may result in increased phenytoin serum levels.

Corticosteroids: Betamethasone, Cortisone, Dexamethasone, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone (Moderate)

Carbamazepine increases corticosteroid metabolism and can decrease effectiveness. Monitor therapeutic efficacy of the corticosteroid. An increase in the steroid dosage may be required after three to five days of concurrent carbamazepine therapy. **Phenytoin also increases the hepatic metabolism of corticosteroids and can decrease effectiveness.**

Benzodiazepines: lorazepam and diazepam (Minor)

Levels of these two agents may be increased by valproic acid.

Bupropion (Minor)

Carbamazepine and phenytoin decrease bupropion effectiveness secondary to induction of bupropion metabolism

Candesartan (Minor)

Additive hyponatremic effects when given concurrently with carbamazepine

Carbamazepine

Concurrent carbamazepine and lamotrigine may result in reduced lamotrigine efficacy. Concurrent carbamazepine and phenytoin may result in increased or decreased phenytoin levels and decreased carbamazepine concentration.(Minimal)

Concurrent carbamazepine and valproic acid may result in decreased serum valproic acid levels (Moderate).

Caspofungin (Moderate)

Carbamazepine or phenytoin reduces caspofungin plasma levels. An increase in the dose of caspofungin to 70 mg daily is suggested in patients with candidal esophagitis or aspergillosis who are not responding to 50 mg daily during combined carbamazepine/phenytoin therapy.

Chloramphenicol (Moderate)

Chloramphenicol may decrease phenytoin metabolism and result in phenytoin toxicity.

Chlorpromazine (Minimal)

Concurrent use with phenytoin may result in increased or decreased phenytoin levels.

Chlorpromazine may cause an increase in valproic acid levels.

Cimetidine (Moderate)

Cimetidine may decrease carbamazepine metabolism. Monitor carbamazepine levels if cimetidine is added or withdrawn from therapy. Cimetidine may inhibit metabolism of phenytoin or valproic acid leading to increased levels.

Ciprofloxacin (Moderate)

Ciprofloxacin may increase or decrease phenytoin levels.

Clarithromycin (Moderate)

Concurrent clarithromycin and valproic acid may increase valproic acid levels. Clarithromycin may decrease carbamazepine metabolism. Decrease the carbamazepine dose by approximately 25% at the initiation of clarithromycin therapy with further modification according to clinical symptoms and serum carbamazepine trough concentrations. Concomitant clarithromycin and phenytoin may result in increased phenytoin levels. Concurrent clarithromycin and valproic acid may increase valproic acid levels.

Clomipramine (Moderate)

Unlike other tricyclic antidepressants, carbamazepine may raise clomipramine levels. The clinical importance is not clear.

Clonazepam (Minimal)

Carbamazepine may induce clonazepam hepatic metabolism resulting in reduced plasma levels. Seizure control and clonazepam levels should be monitored whenever carbamazepine is added or withdrawn from therapy, or when the carbamazepine dose is changed. Concurrent clonazepam and phenytoin may result in alterations of either medication.

Clorgyline, Isocarboxazid, Moclobemide, Pargyline, Phenelzine, Selegiline, Tranylcypromine (Major)

The concurrent administration of carbamazepine and monoamine oxidase inhibitors (e.g., clorgyline, **Isocarboxazid**) can result in hypertensive urgency, hyperpyrexia, and seizures. Monoamine oxidase inhibitors should be discontinued for a minimum of 14 days before carbamazepine therapy is initiated.

Clozapine (Major)

Avoid concurrent use of carbamazepine and clozapine. There is an increased risk of bone marrow suppression, asterixis, or decreased serum clozapine levels. Phenytoin and valproic acid may decrease clozapine plasma levels.

Oral Contraceptives- Estradiol, Ethinyl estradiol, levonorgestrel, mestranol, norethindrone, norgestrel (Minimal)

Carbamazepine, oxcarbazepine, and phenytoin increase the metabolism of contraceptive steroids, which can decrease contraceptive effectiveness.

Cyclosporine (Moderate)

Carbamazepine, phenobarbital or phenytoin reduce cyclosporine serum levels and potentially increases the risk for organ rejection

Cytotoxic agents- Bleomycin, carboplatin, carmustine, methotrexate, vinblastine, vincristine (Moderate)

May alter phenytoin bioavailability resulting in decreased phenytoin effectiveness.

Danazol (Moderate)

Danazol decreases carbamazepine metabolism and toxicity may result unless carbamazepine dose is reduced.

Delaviridine (Moderate)

Concurrent use of phenytoin and delaviridine can decrease delaviridine concentrations and decrease efficacy.

Desipramine (Moderate)

Increased carbamazepine toxicity and decreased desipramine effectiveness

Dexmethylphenidate (Moderate)

Concurrent use with phenytoin results in increased phenytoin plasma concentrations.

Diltiazem (Moderate)

Diltiazem decreases carbamazepine and phenytoin metabolism and toxicity may result.

Disopyramide (Moderate)

Phenytoin reduces disopyramide concentrations by 25% to 75%.

Disulfiram (Severe)

Disulfiram decreases phenytoin metabolism and increases phenytoin toxicity.

Digoxin, digitoxin (Moderate)

Phenytoin increases the clearance of digoxin and digitoxin resulting in decreased serum concentrations

Donepezil (Minor)

Avoid using cytochrome p450 inducers such as phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital in donepezil treated patients.

Doxepin (Moderate)

Decreased doxepin effectiveness and possibly increased carbamazepine toxicity

Doxycycline (Moderate)

Chronic carbamazepine therapy may decrease the half-life of doxycycline by 50%. Phenytoin may decrease half-life and lower serum levels of doxycycline.

Erythromycin (Severe)

Erythromycin decreases the hepatic clearance of carbamazepine causing elevated carbamazepine serum concentrations. The combination of carbamazepine and macrolide antibiotics should be avoided. If the combination is necessary, carbamazepine levels should be obtained within two days of adding or discontinuing erythromycin and dosage adjustments made accordingly. Valproic acid and erythromycin may result in increased valproic acid levels. (Moderate)

Ethosuximide (Minimal)

Patients receiving concurrent therapy with carbamazepine or phenytoin and ethosuximide may achieve lower serum ethosuximide concentrations. Concomitant valproic acid and ethosuximide may either increase, decrease or not change drug levels.

Felbamate (Moderate)

Concurrent therapy may result in decreased carbamazepine or felbamate effectiveness. Concurrent felbamate and phenytoin may result in decreased phenytoin metabolism and increased felbamate metabolism. Concurrent felbamate and valproic acid may increase valproic acid drug concentrations.

Felodipine (Minor)

Concurrent therapy with carbamazepine, oxcarbazepine or phenytoin and felodipine may result in decreased levels of felodipine.

Fluconazole (Severe)

Fluconazole inhibits cytochrome p450 3a4-mediated metabolism resulting in an increased risk of carbamazepine or phenytoin toxicity

Fluoxetine, Sertraline, Fluvoxamine (Moderate)

Concurrent use of these SSRIs and carbamazepine may result in carbamazepine toxicity secondary to decreased carbamazepine metabolism. Concurrent phenytoin with either fluoxetine or fluvoxamine may increase risk of phenytoin toxicity. Sertraline may decrease lamotrigine or phenytoin metabolism resulting in increased risk of toxicity. Serum valproic acid levels may be increased by concurrent fluoxetine use.

Haloperidol

Carbamazepine can increase haloperidol metabolism resulting in decreased haloperidol effectiveness. Higher haloperidol dosage may be required in some clinical situations.

Hydrochlorothiazide (Minor)

Additive hyponatremic effect when given with carbamazepine.

Ibuprofen

Concurrent phenytoin and ibuprofen may result in increased phenytoin levels.

Imatinib (Minor)

Concurrent use with phenytoin results in decreased concentration of imatinib.

Imipramine (Minor)

Carbamazepine increases imipramine metabolism, which may decrease imipramine effectiveness

Imipramine inhibits phenytoin metabolism and may result in increased phenytoin levels.

Indinavir (Moderate)

Carbamazepine induces cytochrome p450 3a4-mediated indinavir metabolism. Alternatives to carbamazepine therapy should be considered. Phenytoin can decrease indinavir plasma concentrations.

Isoniazid (Moderate)

Concomitant carbamazepine and isoniazid therapy may increase carbamazepine serum concentrations.

Monitor carbamazepine levels during concurrent use of these agents. Concomitant phenytoin and isoniazid may increase phenytoin serum concentrations. Monitor patients on concurrent valproic acid and isoniazid for hepatic and CNS toxicity. (minimal)

Isotretinoin (Minimal)

Isotretinoin may decrease carbamazepine levels.

Itraconazole (Moderate)

Carbamazepine or phenytoin induce itraconazole metabolism and may decrease effectiveness.

Ketoconazole (Minimal)

Ketoconazole inhibits carbamazepine metabolism. Close monitoring of carbamazepine serum concentrations is recommended when ketoconazole therapy is initiated in a patient stabilized on carbamazepine. Dose reductions of carbamazepine may be necessary.

Lamotrigine (Moderate)

Concurrent lamotrigine therapy with carbamazepine, oxcarbazepine or phenytoin may reduce lamotrigine efficacy and increase risk of neurotoxicity. Concurrent lamotrigine and valproic acid may result in increased lamotrigine levels and decreased valproic acid levels.

Levodopa (minimal)

Concurrent phenytoin and levodopa may result in decreased levodopa effectiveness.

Levomethadyl (Moderate)

Phenytoin induces CYP 3A4 and concurrent use with levomethadyl may result in QT prolongation.

Lithium (Moderate)

Concurrent carbamazepine and lithium may result in additive neurotoxicity.

Concurrent phenytoin and lithium may result in additive toxicity.

Maprotiline (Minor)

Concurrent carbamazepine and maprotiline therapy results in decreased maprotiline levels and increased carbamazepine levels

Mebendazole (Moderate)

Carbamazepine or phenytoin may decrease mebendazole effectiveness

Meperidine (Moderate)

Phenytoin increases meperidine clearance resulting in decreased meperidine effectiveness.

Methadone (Minor)

Higher methadone doses may be required in patients taking enzyme-inducing medications such as carbamazepine or phenytoin.

Methoxsalen (Moderate)

Phenytoin may decrease levels of methoxsalen.

Methsuximide (Moderate)

Methsuximide induces hepatic metabolism of lamotrigine and concurrent use results in decreased lamotrigine serum concentrations. Concurrent use of phenytoin with methsuximide results in increased phenytoin levels.

Methylphenidate (Minimal)

Carbamazepine induces the metabolism of methylphenidate and may result in loss of methylphenidate efficacy. Methylphenidate raises serum phenytoin levels. Concurrent methylphenidate and valproic acid increases the risk of valproic acid adverse effects and CNS toxicity.

Metronidazole (Moderate)

Concurrent metronidazole and carbamazepine may result in increased carbamazepine serum concentrations and potential carbamazepine toxicity.(moderate) Concurrent metronidazole and phenytoin may result in increased risk of phenytoin toxicity and decreased metronidazole plasma levels.(minimal)

Miconazole (Moderate)

Concurrent miconazole and phenytoin may increase risk of phenytoin toxicity.

Naproxen (Minimal)

Naproxen displaces valproic acid from protein bound sites thereby increasing the clearance of total drug but leaving free valproic acid levels unchanged. Monitor for valproic acid toxicity.

Nefazodone

Concurrent nefazodone and carbamazepine may result in increased carbamazepine serum concentrations and potential carbamazepine toxicity.

Nelfinavir (Moderate)

Concurrent nelfinavir and carbamazepine or phenytoin may result in decreased nelfinavir plasma concentrations. Dosing adjustments may be necessary.

Nifedipine (Moderate)

Nifedipine may decrease phenytoin metabolism and increase toxicity.

Nimodipine (Minor)

Carbamazepine or phenytoin induces nimodipine metabolism and may decrease its effectiveness. Nimodipine levels may be raised by valproic acid.

Nisoldipine (Moderate)

Phenytoin induces nisoldipine metabolism and results in decreased plasma concentrations.

Olanzapine (Moderate)

Carbamazepine induces olanzapine metabolism and may decrease its effectiveness.

Omeprazole (Moderate)

Omeprazole inhibits carbamazepine metabolism and concurrent use may increase the risk of carbamazepine toxicity. Omeprazole may increase the concentration of phenytoin.

Oxcarbazepine (Moderate)

Concurrent oxcarbazepine and lamotrigine may result in reduced lamotrigine concentrations.

Concurrent oxcarbazepine and phenytoin may result in increased phenytoin concentrations.

Concurrent oxcarbazepine and valproic acid may result in decreased oxcarbazepine levels.

Phenobarbital, Primidone (Minimal)

Concurrent use of phenobarbital and carbamazepine may decrease carbamazepine effectiveness with loss of seizure control. Concurrent phenobarbital and phenytoin may result in altered phenytoin levels. Concurrent phenobarbital and lamotrigine enhances lamotrigine clearance and may result in reduced lamotrigine efficacy. Concurrent phenobarbital and oxcarbazepine may increase phenobarbital levels by 14%. Concurrent phenobarbital and valproic acid may result in increased phenobarbital levels and decreased valproic acid levels.

Phenytoin

Concurrent carbamazepine and phenytoin may either decrease or increase phenytoin concentrations and decrease carbamazepine concentrations. Concurrent gabapentin and phenytoin may result in increased phenytoin levels. Concurrent lamotrigine and phenytoin may result in decreased lamotrigine efficacy. Concurrent phenytoin and oxcarbazepine may result in increased phenytoin levels by 40%. Concurrent primidone and phenytoin may lead to elevated phenobarbital concentrations.

Praziquantel (Moderate)

Carbamazepine increases praziquantel metabolism and may decrease its effectiveness.

Pregabalin

Pharmacokinetic drug interactions have not been reported to date.

Propoxyphene (Moderate)

Propoxyphene decreases carbamazepine metabolism and concurrent use may increase the risk of carbamazepine toxicity. Use of an alternative analgesic, such as a codeine or hydrocodone, should be considered.

Quinupristin/dalfopristin (Moderate)

Quinupristin/dalfopristin may inhibit carbamazepine metabolism. Monitor the trough carbamazepine concentrations when therapy with quinupristin/dalfopristin is administered concurrently.

Quetiapine (Moderate)

Phenytoin increases the clearance of quetiapine and may decrease efficacy.

Quinidine(Moderate)

Phenytoin increases quinidine metabolism

Rifampin (Minimal)

Rifampin inhibits carbamazepine metabolism and concurrent use may result in elevated carbamazepine levels and toxicity. Rifampin may reduce lamotrigine or valproic acid concentrations. Rifampin may increase phenytoin clearance and reduce serum concentrations. (moderate)

Risperidone (Moderate)

Carbamazepine increases risperidone metabolism; higher risperidone doses may be needed.

Risperidone may increase valproic acid levels.

Ritonavir (Moderate)

Ritonavir decreases carbamazepine metabolism and concurrent use may increase the risk of carbamazepine toxicity. Concurrent ritonavir and lamotrigine result in decreased lamotrigine serum concentrations. Concurrent ritonavir and valproic acid result in decreased valproic acid levels.

Saquinavir (Moderate)

Carbamazepine or phenytoin induces saquinavir metabolism and concurrent use may result in reduced saquinavir effectiveness.

Sirolimus (Moderate)

Concurrent use of carbamazepine or phenytoin with either sirolimus or tacrolimus may result in loss of sirolimus or tacrolimus efficacy.

Sucralfate (Moderate)

Sucralfate may decrease phenytoin absorption, separate administration by 2 hours.

Theophylline (Moderate)

Carbamazepine increases theophylline metabolism.

Tiagabine (Moderate)

Carbamazepine, phenytoin, phenobarbital and primidone induce tiagabine metabolism and may result in decreased tiagabine efficacy. Concurrent valproic acid and tiagabine may result in increased tiagabine adverse reactions.

Ticlopidine (Moderate)

Ticlopidine decreases carbamazepine and phenytoin metabolism and concurrent use may increase the risk of toxicity.

Topiramate (Moderate)

Carbamazepine increases topiramate clearance and may result in decreased topiramate concentrations. Concurrent topiramate and valproic acid result in decreased topiramate concentrations and decreased valproic acid concentrations.

Tramadol (Moderate)

Carbamazepine induces tramadol metabolism and concurrent use may result in decreased tramadol efficacy.

Trazodone (Minimal)

Trazodone inhibits carbamazepine metabolism; concurrent use may increase the risk of carbamazepine toxicity. Trazodone may increase phenytoin levels.

Trimethoprim (Moderate)

Trimethoprim may decrease phenytoin clearance and increase the risk of toxicity.

Troleandomycin (Moderate)

Troleandomycin inhibits carbamazepine metabolism; concurrent use may increase the risk of carbamazepine toxicity.

Valproic acid (Minimal)

Concurrent valproic acid and carbamazepine therapy may result in carbamazepine toxicity and/or decreased valproic acid effectiveness. Tiagabine decreases valproic acid concentrations about 10%. Concurrent valproic acid and lamotrigine may result in lamotrigine toxicity.

Verapamil (Moderate)

Verapamil decreases carbamazepine metabolism; concurrent use may increase the risk of carbamazepine toxicity. Monitor carbamazepine levels when given with verapamil.

Vigabatrin (Major)

Vigabatrin decreases carbamazepine metabolism; concurrent use may increase the risk of carbamazepine toxicity.

Warfarin (Moderate)

Carbamazepine increases warfarin metabolism and concurrent use may result in decreased anticoagulant effectiveness.

Zidovudine (Moderate)

Valproic acid increases the bioavailability of zidovudine.

Zonisamide (Minor)

Carbamazepine induces zonisamide metabolism and concurrent therapy may result in decreased zonisamide plasma concentrations.

6. Drug-disease interactions

a. Rash¹⁶⁷⁻¹⁷¹

Serious dermatologic reactions can occur with many of the anticonvulsant agents. Lamotrigine has a black box warning in its product labeling regarding the incidence of serious rashes. These rashes including Stevens-Johnson Syndrome occur in 1% of pediatric patients treated with lamotrigine and in 0.3% in adults. The risk of rash may be increased in patients concomitantly treated with valproic acid, or when the starting dose exceeds the manufacturer recommendations, or the dose is escalated too quickly. Nearly all cases occur within the first 2 to 8 weeks of starting treatment. If a rash develops, treatment with lamotrigine should be discontinued immediately.

Zonisamide, a sulfonamide, may also cause serious skin rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis. In clinical trials, 2.2% of patients discontinued zonisamide because of a rash.

Serious rash, including Stevens-Johnson syndrome, has also been reported with tiagabine and oxcarbazepine therapy. In clinical trials, 5% of tiagabine treated patients developed a rash compared to 4% of placebo treated patients.

Phenytoin is well-known to cause rash. If the rash is exfoliative, purpuric, bullous or if Stevens-Johnson syndrome, lupus erythematosus, or toxic epidermal necrolysis is suspected, the drug should be stopped and not resumed. If the rash is measles-like, phenytoin therapy may be reinitiated after the rash has completely resolved.

b. Liver disease¹⁷²

Hepatic failure resulting in death has occurred in patients treated with valproic acid. Children under 2 years of age are at an increased risk for developing hepatotoxicity. This reaction usually occurs during the first six months of treatment. Life threatening pancreatitis has also been reported with valproic acid. Both hepatotoxicity and pancreatitis are listed in the product labeling as black box warnings.

c. Renal disease^{39, 50}

Both gabapentin and pregabalin are eliminated via renal excretion as unchanged drug. Doses of both agents must be reduced in patients with creatinine clearances < 60 mL/min.

d. Hematologic Abnormalities^{17, 39, 172}

Carbamazepine may rarely cause aplastic anemia and agranulocytosis. Carbamazepine should not be used in patients with a history of bone marrow depression. If a patient has a decreased white blood cell count or platelet count while being treated with carbamazepine, the patient should be monitored closely for significant bone marrow depression.

Thrombocytopenia is a dose-related adverse event that occurs in patients treated with valproic acid. In clinical trials, 24% to 27% of patients treated with valproic acid had platelet counts less than or equal to $75 \times 10^9/L$.

Decreased platelet counts, defined as 20% below baseline and $< 150 \times 10^3/\mu L$, were reported in 3% of patients treated with pregabalin compared with 2% of patients on placebo.

e. Hyponatremia¹⁷¹

Significant hyponatremia, defined as a serum sodium less than 125 mmol/L, can develop in patients treated with oxcarbazepine. Hyponatremia generally occurs within the first 3 months of therapy but can develop after more than a year of treatment. Patients on diuretic therapy may have additive hyponatremia when started on oxcarbazepine.

f. Oligohidrosis and hyperthermia^{168, 173, 174}

The product labeling for zonisamide was recently changed to reflect the risk of oligohidrosis and hyperthermia in patients prescribed zonisamide. There have been 40 reported cases of this adverse reaction. Pediatric patients appear to be at an increased risk for decreased sweating and increased body temperature. Patients should be monitored closely for evidence of decreased sweating and increased body temperature, especially in warm weather.

Oligohidrosis and hyperthermia have also been reported in patients, primarily children, taking topiramate.

g. Pancreatitis¹⁷²

The product labeling for pregabalin states that pancreatitis is a rare side effect. Pancreatitis has also been reported post-marketing with zonisamide (<1:1000).

h. Ophthalmologic Effects^{39, 174}

Visual disturbances, including blurred vision and decreased ability to drive, have been reported in patients taking pregabalin. Patients should be advised to avoid driving or operating machinery if they experience these symptoms.

Acute myopia and secondary angle closure glaucoma have been reported in patients taking topiramate. Symptoms usually occur within 1 month of starting therapy. Both adults and children can develop the secondary angle closure glaucoma.

i. Congestive heart failure³⁹

Pregabalin should be used with caution in patients with Class III or IV heart failure. Weight gain and peripheral edema can occur. In clinical trials peripheral edema occurred in 6% of patients taking pregabalin compared to 2% in placebo group. Weight gain of 7% over baseline was reported in 8% of pregabalin treated patients and 2% of placebo treated patients. Weight gain and peripheral edema occur more frequently when patients are concomitantly taking thiazolidinedione antidiabetic agents.

j. Metabolic acidosis¹⁷⁴

Topiramate can cause a decrease in serum bicarbonate levels and lead to the development of hyperchloremic, non-anion gap metabolic acidosis. The incidence of treatment-emergent decreases in sodium bicarbonate have ranged from 20% to 44% in clinical trials.

5. Recommendations

Available evidence suggests that pregabalin could be reserved for patients who have failed tricyclic antidepressants (amitriptyline, nortriptyline, desipramine) or their use is contraindicated and failed gabapentin (minimum dose 1200 mg/day) for the treatment of diabetic peripheral neuropathy. Until cost-effectiveness studies are published showing that pregabalin is beneficial and cost-effective as first-line therapy, a conservative approach using tricyclic antidepressants and gabapentin is reasonable. The disadvantage in this recommendation is that neither gabapentin nor tricyclic antidepressants are FDA-labeled for DPN, while pregabalin has this labeling.

For postherpetic neuralgia, both gabapentin and pregabalin are FDA-labeled for treatment. Given there are no head-to-head comparative studies showing superior efficacy of one agent over another, it is reasonable to choose the less expensive agent as preferred therapy and have the more expensive agent on prior authorization.

For patients with trigeminal neuralgia, carbamazepine is the drug of choice. Any other anticonvulsant selected for this indication should be reserved for prior authorization.

Carbamazepine (Tegretol®, Tegretol XR®, generic) ^{17, 164, 165, 175, 176 ,177}

	Criteria		Rationale
Maximum dose per day	Trigeminal neuralgia- 1200 mg/day Epilepsy- generally not to exceed 1200 mg/day, rare cases where need 1600 mg/day		Based on maximal doses in product labeling.
Indication for use	Labeled: Partial seizures with complex symptoms, generalized tonic-clonic seizures, mixed seizure patterns or partial or generalized seizures Trigeminal neuralgia		Supported by product labeling.
	Unlabeled: Peripheral neuropathic pain ^{6, 60-63,84} Restless legs syndrome ^{65, 66} Bipolar disorder ^{3, 178-180} Management of alcohol and drug withdrawal ^{181-186 187} Cochrane review found no evidence for use in cocaine dependence. ¹⁸²		Use has been evaluated in properly randomized clinical trials. 11 randomized trials have evaluated the efficacy of CBZ in neuropathic pain. Carbamazepine is superior to placebo and equal in efficacy to Phenobarbital and oxazepam for patients with mild to moderate alcohol withdrawal symptoms.
	Hereditary and nonhereditary chorea ⁶⁸⁻⁷⁰ Dyscontrol syndrome with limbic system dysfunction ^{133, 188, 189} Schizoaffective illness ¹⁹⁰		Use has been evaluated in clinical trials that were either non-randomized, open-labeled, case-control or cohort studies or uncontrolled experiments.
	Phantom limb pain ⁶⁷ Intermittent explosive disorder ^{191, 192} Post-traumatic stress disorder ^{133, 134, 193-196,197} Atypical psychosis ^{198, 199}		Use based from descriptive reports or case studies
Drug-drug interactions	Monoamine oxidase inhibitors		Concomitant use is contraindicated
	Acetaminophen Clozapine Diuretics Candesartan Lithium		Toxicity may be increased by concomitant carbamazepine administration
	Amprenavir Cimetidine Clarithromycin Danazol Desipramine Diltiazem Doxepin Erythromycin Fluconazole Fluoxetine Fluvoxamine Isoniazid Ketoconazole Maprotiline Metronidazole	Nefazodone Omeprazole Propoxyphene Protriptyline Quinupristin/dalfopristin Rifampin Ritonavir Sertraline Ticlodipine Trazodone Troleandomycin Valproic acid Verapamil Vigabatrin	Increased pharmacologic effects of carbamazepine when given concurrently
	Acetylcysteine Activated charcoal Felbamate Pentobarbital		Decreased pharmacologic action of carbamazepine when given concurrently with these medications

	Phenytoin Primidone/phenobarbital		
	Alprazolam Amitriptyline Amoxapine Amprenavir Anticoagulants Corticosteroids Bupropion Caspofungin Clomipramine Clonazepam Clozapine Oral contraceptives Cyclosporine Donepezil Doxepin Doxycycline Ethosuximide Felbamate Felodipine Haloperidol Imipramine Indinavir Itraconazole	Lamotrigine Maprotiline Mebendazole Methadone Methylphenidate Nelfinavir Nimodipine Nortriptyline Olanzapine Praziquantel Protriptyline Risperidone Saquinavir Sirolimus Tacrolimus Theophylline Tiagabine Topiramate Tramadol Trimipramine Valproic acid Warfarin Zonisamide	Carbamazepine may decrease the pharmacologic effects of these medications if given concurrently
Drug-disease interactions	Liver dysfunction		Monitor liver function tests periodically.
	Elderly patients		Clearance of carbamazepine is reduced and lower maintenance dose may be required.
	History of bone marrow depression		Leukopenia is observed in 10% - 20% of patients. Persistent leukopenia in 2% of patients. Thrombocytopenia, aplastic anemia and agranulocytosis have been reported.
	Absence seizures		Carbamazepine can exacerbate absence seizures in children.
	Psychosis		Patients with underlying mental illness may experience activation of latent psychosis or agitation.
	History of cardiac damage.		Carbamazepine is an anticonvulsant structurally related to the tricyclic antidepressants. As with other tricyclic compounds, carbamazepine may cause disturbances in cardiac conduction including sinus tachycardia, bradyarrhythmias or atrioventricular conduction delay. Hypertension, hypotension, and edema have been reported.
	Seizure disorders		Abrupt withdrawal may precipitate status epilepticus.

	Criteria	Rationale
Maximum dose per day	Epilepsy 3600 mg/day Post-herpetic neuralgia 3600 mg/day	Safety has not been assessed at higher doses. For post-herpetic neuralgia, additional benefit of doses > 1800 mg/day has not been demonstrated.
Indication for use	Labeled: Adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients > 12 years of age with epilepsy. Also indicated as adjunctive therapy for partial seizures in children 3 to 12 yrs of age. Post-herpetic neuralgia	Supported by product labeling.
	Unlabeled: Diabetic neuropathy ^{71 72, 73} Migraine prophylaxis ⁷⁹ Multiple Sclerosis ⁸² Bipolar mania ²⁰⁰⁻²⁰⁹ Social phobia ²¹⁰ Panic disorder ²¹¹	Use has been evaluated in properly randomized clinical trials.
	Trigeminal neuralgia ⁷³	Use has been evaluated in clinical trials that were either non-randomized, open-labeled, case-control or cohort studies or uncontrolled experiments.
	Central pain ⁷³ Neuropathic cancer pain ⁷³ HIV polyneuropathy ⁷³	Use based from descriptive reports or case studies.
Drug-drug interactions	Antacids- separate by 2 hours	Decreased pharmacologic action of gabapentin when given concurrently with these medications
Drug-disease interactions	Renal insufficiency	Reduce dosage in patients with impaired renal function.
	Seizure disorders	Abrupt withdrawal may precipitate status epilepticus.

Lamotrigine (Lamictal®) ^{170, 164, 165, 175, 176, 177}

	Criteria	Rationale
Maximum dose per day	Epilepsy 500 mg/day If added to valproic acid, maximum dose is 200 mg/day. Bipolar disorder 200 mg/day If added to valproic acid, maximum dose is 100 mg/day. If added to carbamazepine, phenytoin, phenobarbital, primidone, or rifampin 400 mg/day.	Product labeling indicates 500 mg/day is maximal dose. Some patients with partial seizures have required up to 700 mg/day.
Indication for use	Labeled: Adjunctive or monotherapy therapy in the treatment of partial seizures Adjunctive therapy in generalized seizures of Lennox-Gastaut syndrome Bipolar disorder	Supported by product labeling
	Unlabeled: Neuropathic pain ^{45, 83, 84} HIV-associated polyneuropathy ⁸³ Trigeminal neuralgia ^{18, 21, 24,} ₂₅ Central poststroke pain ⁸⁵	Use has been evaluated in properly randomized clinical trials.
	Phantom limb pain ⁸⁶	Use based from descriptive reports or case studies.
Drug-drug interactions	Alcohol	Enhanced CNS depression
	Carbamazepine Phenobarbital Phenytoin Fosphenytoin Primidone Methsuximide Oxcarbazepine Rifampin Ritonavir	Decreased pharmacologic action of lamotrigine when given concurrently with these medications
	Sertraline Valproic acid	Lamotrigine toxicity has been reported with concomitant use
Drug-disease interactions	Discontinue therapy at the first sign of a rash (black-box warning)	Rash occurs in 10% of patients. Life threatening rashes occur in 1:1000 in adults and 1:100 in children. Risk factors for rash include rapid dose escalation, high initial dosage and concomitant valproic acid therapy.
	Renal impairment	Dose reduction required for patients with renal impairment.
	Seizure disorders	Abrupt withdrawal may precipitate status epilepticus.

Levetiracetam (Keppra®) ^{212, 164, 165, 175, 176, 177},

	Criteria	Rationale
Maximum dose per day	3000 mg/day	Safety and efficacy at higher doses has not been assessed
Indication for use	<p>Labeled: Adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy</p> <p>Unlabeled: Autism. ¹⁵⁰ Acute mania ¹⁵¹</p>	<p>Supported by product labeling</p> <p>There is only one published case report of levetiracetam being successfully used to treat acute mania. ¹⁵¹</p> <p>One open-label study in 10 autistic male children ages 4 – 10 yrs given levetiracetam. May reduce hyperactivity, impulsivity and mood instability but further study is needed. ¹⁵⁰</p>
Drug-drug interactions	None	Levetiracetam has no known drug-drug interactions.
Drug-disease interactions	Renal impairment Elderly patients	Dosage adjustment required Reduce starting dose by one-half.
	Seizure disorders	Abrupt withdrawal may precipitate status epilepticus.

Oxcarbazepine (Trileptal®) ^{171, 164, 165, 175, 176, 177}

	Criteria	Rationale
Maximum dose per day	2400 mg/day	Safety at higher doses has not been assessed
Indication for use	Labeled: Monotherapy or adjunctive therapy in the treatment of partial seizures in adults Adjunctive therapy in the treatment of partial seizures in children 4-16 yrs old	Supported by product labeling
	Unlabeled: Bipolar disorder ¹⁵²⁻¹⁵⁵ Diabetic peripheral neuropathy Trigeminal neuralgia ^{19, 22, 26} Notalgia paresthetica ¹⁵⁶	Use has been evaluated in clinical trials that were either non-randomized, open-labeled, case-control or cohort studies or uncontrolled experiments.
Drug-drug interactions	Carbamazepine Valproic acid	Decreased pharmacologic action of oxcarbazepine when given concurrently with these medications
	Phenobarbital- increased concentrations by 14% Phenytoin- increased concentrations by 40% Fosphenytoin	Oxcarbazepine may increase the serum levels of these medications if given concurrently
	Alcohol	Toxicity may be increased by concomitant oxcarbazepine administration- Additive sedative effects
	Oral contraceptives Felodipine Verapamil	Decreased pharmacologic effects of these medications when given concurrently with oxcarbazepine
Drug-disease interactions	Hypersensitivity to carbamazepine	25% to 30% of patients with allergic reactions to carbamazepine will have hypersensitivity to oxcarbazepine
	Hyponatremia	Hyponatremia occurs in 2.5% of patients; monitor serum sodium.
	Renal impairment	Dosage adjustment required.
	Central nervous system adverse events	Cognitive symptoms such as psychomotor slowing, concentration difficulties, and speech or language problems, somnolence or fatigue, and coordination abnormalities such as ataxia or gait disturbances.
	Seizure disorders	Abrupt withdrawal may precipitate status epilepticus.

Pregabalin (Lyrica®) – Schedule CV ^{39, 164, 165, 176}

	Criteria	Rationale
Maximum dose per day	Epilepsy 600 mg/day Post-herpetic neuralgia 300 mg/day Diabetic peripheral neuropathy 300 mg/day	Safety has not been assessed at higher doses.
Indication for use	Labeled: Adjunctive therapy in the treatment of partial seizures Post-herpetic neuralgia Diabetic peripheral neuropathy	Supported by product labeling.
	Unlabeled: Fibromyalgia Generalized anxiety disorder Social anxiety disorder	Use has been evaluated in randomized clinical trials.
Drug-drug interactions	Thiazolidinediones (rosiglitazone, pioglitazone)	Concomitant use may result in more pronounced weight gain and peripheral edema. This could exacerbate or worsen heart failure.
Drug-disease interactions	Renal impairment	Doses must be reduced in patients with renal impairment and on hemodialysis.
	Epilepsy- Avoid abrupt drug withdrawal	Pregabalin should be withdrawn gradually (over a minimum of 1 week) to minimize the potential of increased seizure frequency. Additionally, abrupt or rapid discontinuation of pregabalin has resulted in insomnia, nausea, headache and diarrhea.
	Ocular effects	Visual disturbances, including blurred and double vision, can occur. Patients should be counseled that if visual changes occur to notify their physician.
	Central Nervous System effects	Dizziness and somnolence most frequently led to drug withdrawal in clinical trials. These adverse effects appear to be dose-related and occur shortly after starting therapy.
	Cardiovascular	Pregabalin should be used cautiously in patients with heart failure (NYHA class III or IV), as it may increase weight gain or fluid retention.
	Rhabdomyolysis and myopathy	Creatine kinase elevations greater than 3X the upper limit of normal occur in 2% of patients treated with pregabalin compared with 1% of patients treated with placebo. Rhabdomyolysis has been reported.

Phenytoin (Dilantin®) ^{169, 164, 165, 175, 176}

	Criteria		Rationale
Maximum dose per day	Therapeutic range is 10 to 20 mcg/mL Provide optimal control of clinical symptoms without signs of clinical toxicity.		Incidence of adverse effects increases at concentrations above 20 mcg/mL
Indication for use	Labeled: Control of grand mal and psychomotor seizures. Prevent or treat seizures during or after neurosurgery		Supported by product labeling
	Unlabeled: Adjuvant therapy in cancer pain ^{105, 106} Adjuvant therapy in mania ¹¹⁰ Peripheral neuropathic pain ¹¹¹		Use has been evaluated in properly randomized clinical trials.
	Chronic pain ¹⁰⁷⁻¹⁰⁹ Second line for trigeminal neuralgia ^{112, 113}		Use based from descriptive reports or case studies.
	Diabetic neuropathy ^{46, 47, 104}		Evidence not conclusive to support use.
Drug-drug interactions	Barbiturates Carbamazepine Diazoxide Ethanol Rifampin Theophylline Antacids	Charcoal Sucralfate- separate by 2 hours Folic acid Loxapine Nitrofurantoin Pyridoxine Cytotoxic agents (cisplatin, casrmustine, bleomycin, vinblastine)	Decreased pharmacologic action of phenytoin when given concurrently with these medications
	Acetaminophen Amiodarone Carbamazepine Digoxin, digitoxin Corticosteroids Disopyramide Doxycycline Estrogen Haloperidol Methadone Metyrapone Mexiletine Meperidine	Oral Contraceptives Quinidine Valproic acid Cyclosporine Dopamine Furosemide Levodopa Levonorgesterel Mebendazole Phenothiazines (chlorpromazine, prochlorperazine, thioridazine) Sulfonylureas	Phenytoin may decrease the pharmacologic effects of these medications if given concurrently
	Primidone- elevated phenobarbital levels Warfarin- protime may increase or decrease		Toxicity may be increased by concomitant phenytoin administration

	Allopurinol Amiodarone Benzodiazepines Chloramphenicol Cimetidine Diltiazem/nifedipine Disulfiram Fluconazole Isoniazid	Miconazole Sulfonamides Sulfipyrazone Trimethoprim Valproic acid Imipramine Phenothiazines (chlorpromazine, prochlorperazine, thioridazine)	Increased pharmacologic effects of phenytoin when given concurrently
Drug-disease interactions	Pregnancy Febrile Illness Acute traumatic injury		Phenytoin clearance can increase and may require dose adjustment
	Sinus bradycardia, sinoatrial block, second and third degree AV block, Adams-Stokes syndrome		Phenytoin can cause bradycardia; contraindicated to use phenytoin in these conditions
	Chronic renal failure Liver disease Burns Protein malnutrition Nephrotic syndrome Cystic fibrosis		These conditions result in decreased protein binding and an increased volume of distribution. These changes are meaningful with respect to interpretation of total phenytoin concentrations but have little or no therapeutic consequence in terms of maintenance dosage requirements
	Rash		Discontinue if skin rash occurs. Do not resume if rash is exfoliative, purpuric, or bullous, or if lupus erythematosus or Stevens-Johnson syndrome is suspected.
	Diabetes mellitus		Hyperglycemia has occurred in diabetics. Phenytoin is not choice of anticonvulsant for the treatment of diabetic peripheral neuropathy.
	Porphyria		Phenytoin may precipitate acute attacks of porphyria.
	Seizure disorders		Abrupt withdrawal may precipitate status epilepticus.

Tiagabine (Gabitril®) ^{167, 164, 165, 175, 176}

	Criteria	Rationale
Maximum dose per day	56 mg/day	Doses above 56 mg/day have not been adequately evaluated
Indication for use	Labeled: Adjunctive therapy for the treatment of partial seizures for patients 12 years and older/	Supported by product labeling.
	Unlabeled: Sensory neuropathy ¹¹⁴	Use has been evaluated in clinical trials that were either non-randomized, open-labeled, case-control or cohort studies or uncontrolled experiments.
	Spasticity ¹¹⁶ Anxiety ¹⁵⁷	Use based from descriptive reports or case studies.
Drug-drug interactions	Carbamazepine Phenytoin Phenobarbital Primidone	Decreased pharmacologic efficacy of tiagabine when given concurrently with these medications
	Valproic acid	Tiagabine decreases valproic acid concentrations about 10%; also monitor for excessive tiagabine adverse reactions
	Alcohol	Increased CNS depression may occur
Drug-disease interactions	Hepatic impairment History of status epilepticus	Dosage adjustment required May precipitate status epilepticus
	Weakness	Moderately severe to incapacitating generalized weakness has occurred; reduce or discontinue drug.
	Seizures in patients without epilepsy	Postmarketing reports have shown that tiagabine may cause new onset seizures and status epilepticus in patients without epilepsy. Many patients were on medications that lower seizure threshold.

Topiramate (Topamax®) ^{174, 164, 165, 175, 176}

	Criteria	Rationale
Maximum dose per day	Epilepsy: 1600 mg/day Migraine: 200 mg/day	Doses above 1600 mg/day have not been adequately evaluated. Doses above 400 mg/day have not been shown to improve responses in dose-dependent studies.
Indication for use	Labeled: Adjunctive therapy was partial onset seizures, tonic clonic seizures or seizures associated with Lennox-Gastaut syndrome Migraine headache prophylaxis	Supported by product labeling
	Unlabeled: Trigeminal neuralgia ^{20, 24, 27} Binge Eating Disorder ¹¹⁸ Diabetic peripheral neuropathy	Use has been evaluated in properly randomized clinical trials. Studies for DPN have produced mixed results.
	Bipolar disorder ¹⁵⁹⁻¹⁶¹	Use has been evaluated in clinical trials that were either non-randomized, open-labeled, case-control or cohort studies or uncontrolled experiments.
	Cluster headaches ¹¹⁹⁻¹²⁴	Use based from descriptive reports or case studies.
Drug-drug interactions	CNS depressing medications Alcohol	Increased CNS depression may occur
	Carbamazepine Phenytoin Valproic acid	Topiramate concentrations decreased
	Carbonic anhydrase inhibitors	Concurrent use may increase risk of renal stone formation
	Oral contraceptives	Effectiveness of oral contraceptives may be decreased
	Digoxin	Digoxin concentrations decreased 12%
Drug-disease interactions	Hepatic impairment Renal impairment	Dosage adjustments required in patients with renal or hepatic dysfunction
	Behavioral disorders or cognitive deficits	Psychomotor slowing and difficulty with concentration are the most common reasons for discontinuation.
	Seizure disorders	Abrupt withdrawal may precipitate status epilepticus.
	Predisposition to kidney stones	Renal calculi develop in 1.5% of patients
	Visual disturbances	May cause acute myopia and secondary angle closure glaucoma

Valproic Acid (Depakote®, Depakene®) ^{172, 164, 165, 175, 176}

	Criteria	Rationale
Maximum dose per day	Epilepsy and Mania: 60 mg/kg/day Migraine: 1000 mg/day	Safety not established at higher doses. For migraine, no evidence that higher doses (> 1000 mg/day) provide additional benefit.
Indication for use	Labeled: Monotherapy or adjunctive therapy of various seizure types Mania with bipolar disorder Migraine headache prophylaxis	Supported by product labeling
	Cancer-related neuropathic pain ¹³¹ Diabetic neuropathy ¹³² Alcohol withdrawal ^{187, 129, 130}	Use has been evaluated in properly randomized clinical trials.
	Trigeminal neuralgia ^{127, 128} Post-traumatic stress disorder ^{133, 134} Cluster headaches ^{135, 136} Chronic Daily Headache ¹³⁷⁻¹³⁹ Sydenham's chorea ⁶⁸ Schizoaffective disorders ^{142, 213}	Use has been evaluated in clinical trials that were either non-randomized, open-labeled, case-control or cohort studies or uncontrolled experiments.
	Panic Disorder ^{140, 141}	Use based from descriptive reports or case studies.
Drug-drug interactions	Alcohol	Additive CNS depression
	Tricyclic antidepressants, bupropion, MAO inhibitors, clozapine, haloperidol, loxapine, maprotiline, molidone, phenothiazines, pimozide or thioxanthenes	These medications lower seizure thresholds; dosage adjustments may be necessary
	Clonazepam	Concurrent use may cause absence seizures
	Carbamazepine Cholestyramine Fluoxetine Lamotrigine Mefloquine Phenobarbital Phenytoin Rifampin Ritonavir Topiramate	Decreased pharmacologic action of valproic acid when given concurrently with these medications
	Aspirin Clarithromycin Erythromycin Felbmate Fluoxetine	Increased pharmacologic effects of valproic acid when given concurrently

	Isoniazid	
	Carbamazepine Tiagabine	Toxicity may be increased by concomitant valproic acid administration
	Oxcarbazepine Topiramate Ethosuximide	Valproic acid may decrease the pharmacologic effects of these medications if given concurrently
	Amitriptyline Nortriptyline Clomipramine Diazepam Ethosuximide Lamotrigine Lorazepam Nimodipine Phenobarbital Phenytoin Zidovudine	Valproic acid may increase the pharmacologic effects of these medications if given concurrently
Drug-disease interactions	Hepatic impairment Renal impairment Hypoalbuminemia Pregnancy	May alter clearance of valproic acid.
	Hepatic disease or severe hepatic dysfunction	Liver failure may rarely occur (1 in 40,000); greatest risk during the first 6 months of therapy and in children less than 2 years old who are on multiple anticonvulsants.
	Seizure disorders	Abrupt withdrawal may precipitate status epilepticus.
	Elderly patients	Reduce starting dose
	Pancreatitis	Life-threatening pancreatitis have been reported in both children and adults.

Zonisamide (Zonegran®) ^{168, 164, 165, 175, 176}

	Criteria	Rationale
Maximum dose per day	600 mg per day	Safety not established at higher doses.
Indication for use	Labeled: Adjunctive therapy in the treatment of partial seizures Unlabeled: Bipolar disorder ^{146, 147} Weight loss ¹⁶²	Supported by product labeling. One open-label study in 24 patients showed zonisamide was effective for treating mania. One case report in treating bipolar disorder with zonisamide. A randomized, double-blind, placebo-controlled trial in 60 patients showed zonisamide was more effective than placebo, $p < .001$.
Drug-drug interactions	Carbamazepine Phenobarbital Phenytoin Valproic acid	Increase metabolism and decrease plasma concentrations of zonisamide
	Alcohol or CNS depressants	Additive CNS depression
Drug-disease interactions	Sulfonamide allergy	Avoid in sulfa-allergic patients; potentially fatal reactions to sulfonamides may occur
	Drowsiness and psychomotor slowing, difficulty with concentration, or speech or language problems may occur	CNS adverse reactions are common.
	Seizure disorders	Abrupt withdrawal may precipitate status epilepticus.
	Pediatric patients	Pediatric patients are at an increased risk of oligohidrosis and hyperthermia. Monitor patients for evidence of decreased sweating and increased body temperature.
	Predisposition to kidney stones	Urolithiasis may occur in 2.65 of patients
	Rash	Serious skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis) may occur; discontinuation of zonisamide should be considered
	Renal impairment	Dosage reduction may be needed

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Drug List Appendix

Atypical Antipsychotics

clozapine (Clozaril®)
olanzapine (Zyprexa®)
quetiapine (Seroquel®)
risperidone (Risperdal®)
ziprasidone (Geodon®)

Angiotensin II receptor antagonists

Candesartan cilexetil (Atacand)
Irbesartan (Avapro)
Losartan (Cozaar)
Telmisartan (Micardis)
Valsartan (Diovan)

Antacids

Aluminum hydroxide
Aluminum magnesium hydroxide
Magnesium hydroxide

Anticoagulants

Warfarin (Coumadin®)
Anisindione (Miradon®)
Dicumarol (Dicumarol®)

Anticonvulsants

Gabapentin (Neurontin®)
Pregabalin (Lyrica®)
Phenytoin (Dilantin®)
Fosphenytoin (Cerebyx®)
Carbamazepine (Tegretol®)
Valproic acid (Depakote®, Depakene®)
Primidone (Mysoline)
Lamotrigine (Lamictal®)
Topiramate (Topamax®)
Tiagabine (Gabitril®)
Levetiracetam (Keppra®)
Zonisamide (Zonegran®)
Oxcarbazepine (Trileptal®)

Azole antifungal agents

Fluconazole (Diflucan®)
Itraconazole (Sporanox®)
Ketoconazole (Nizoral®)

Barbiturates

Amobarbital (Amytal)
Aprobarbital (Alurate)
Butabarbital (Butisol, Sarisol)

Mephobarbital (Mebaral)
Methohexital (Brevital)
Pentobarbital (Nembutal)
Phenobarbital (Solfoton, Lumioal, Barbital)
Secobarbital (Seconal)
Thiopental (Pentothal)

Benzodiazepines

Alprazolam (Xanax)
Chlordiazepoxide (Librium, Libritabs, Mitran, Reposans-10)
Clonazepam (Klonopin)
Clorazepate (Tranxene, Gen-Xene)
Diazepam (Valium)
Estazolam (Prosom)
Flurazepam (Dalmane)
Halazepam (Paxipam)
Lorazepam (Ativan)
Oxazepam (Serax)
Prazepam (Centrax)
Quazepam (Doral)
Temazepam (Restoril)
Triazolam (Halcion)

Central Nervous System Depressants

Barbiturates

Amobarbital (Amytal®)
Mephobarbital (Mebaral®)
Pentobarbital (Nembutal®)
Secobarbital (Seconal®)

Carbonic Anhydrase Inhibitors

Acetazolamide (Diamox®)
Dichlorophenamide (Daranide®)
Methazolamide (Neptazane®)

Calcium channel blocking agents

Nisoldipine (Sular)
Nifedipine (Adalat , Procardia)
Nicardipine (Cardene)
Bepridil (Vascor)
Isradipine (DynaCirc)
Felodipine (Plendil)
Amlodipine (Norvasc)
Diltiazem (Cardizem , Dilacor)
Verapamil (Calan , Isoptin)

Corticosteroids

Betamethasone (Celestone®)
Dexamethasone (Decadron®)

Hydrocortisone (Cortisone®)
Prednisone (Deltasone®)
Prednisolone (Prelone®)
Methylprednisolone.(Medrol®)

Diuretics - Thiazides

Chlorothiazide (Diuril®)
Hydrochlorothiazide Esidrex®, Oretic®)
Bendroflumethiazide (Naturetin®)
Methyclothiazide (Enduron®)
Benzthiazide (Exna®)
Indapamide (Lozol®)
Hydroflumethazide (Saluron®)
Trichlormethazide (Naqua®)
Polythiazide (Renese®)
Metolazone (Zaroxolyn®)l
Chlorthalidone (Hygroton®)

Diuretics - Loop

Furosemide (Lasix®)
Bumetanide (Bumex®)
Ethacrynic acid (Edecrin®)
Torsemide (Demadex®)

H2-receptor antagonists

Cimetidine (Tagamet®)
Ranitidine (Zantac®)
Famotidine (Pepcid®)
Nizatidine (Axid®)

Immunosuppressants

Methotrexate (Methotrexate®)
Cyclosporine (Neoral®, Sandimmune®)

Macrolide antibiotics

Azithromycin (Zithromax®)
Clarithromycin (Biaxin®)
Dirithromycin (Dynabac®)
Erythromycin (E-Mycin®, Ery-Tab®, E-Base,
Eryc®, PCE Dispertab®, Ilosone®, E.E.S.
400®, Eryped, Erythrocin®)
Troleandomycin (Tao®)

Miscellaneous agents

Levodopa (Dopar®, Larodopa®)
Lithium (Eskalith®)
Quinidine (Quinidex®, Quinaglute®)
Tramadol (Ultram®)
Trazodone (Desyrel®)
Haloperidol (Haldol®)

Loxapine (Loxitane®)
Molindone (Moban®, Lidone®)
Zolpidem (Ambien®)

Methylxanthines

Caffeine
Theophylline

Monoamine Oxidase Inhibitors

Isocarboxazid (Marplan®)

Phenelzine (Nardil®)

Tranylcypromine (Parnate®)

Non-nucleoside reverse transcriptase inhibitors
(NNRTIs)
Delavirdine (Rescriptor®)

Nonsteroidal anti-inflammatory agents

Indomethacin (Indocin®)
Ibuprofen (Advil®, Motrin®)
Naproxen (Naprosyn®, Naprelan®)
Naproxen sodium (Anaprox®, Aleve®)
Flurbiprofen (Ansaid®)
Ketoprofen (Orudis®)
Ketorolac (Toradol®)
Diflunisal (Dolobid®)
Fenoprofen (Nalfon®)
Oxaprozin (Daypro®)
Diclofenac (Voltaren®)
Etodolac (Lodine®)
Nabumetone (Relafen®)
Sulindac (Clinoril®)
Tolmentin (Tolectin®)
Piroxicam (Feldene®)
Meclofenamate (Meclomen®)
Celecoxib (Celebrex®)
Rofecoxib (Vioxx®)

Phenothiazines

Chlorpromazine (Thorazine®)
Fluphenazine (Prolixin®, Permitil®)
Mesoridazine (Serentil®)
Perphenazine (Trilafon®)
Prochlorperazine (Compazine®)
Thioridazine (Mellaril®)
Thiothixene (Navane®)
Trifluoperazine (Stelazine®)
Promethazine (Phenergan®)

Proton Pump Inhibitors

Omeprazole (Prilosec®)
Lansoprazole (Prevacid®)
Rabeprazole (Aciphex®)
Pantoprazole (Protonix®)

Protease inhibitors

Amprenavir (Agenerase®)
Indinavir (Crixivan®)
Nelfinavir (Viracept®)
Ritonavir (Norvir®)
Saquinavir (Invirase®, Fortovase®)

Oral combination contraceptives

Ethinyl estradiol and desogestrel
Ethinyl estradiol and ethynodiol diacetate
Ethinyl estradiol and levonorgestrel
Ethinyl estradiol and norgestimate
Ethinyl estradiol and norethindrone
Ethinyl estradiol and norgestrel
Mestranol and norethindrone

Oral estrogen products

Diethylstilbestrol
Estradiol
Estradiol and testosterone
Estrogens, conjugated
Estrogens, esterified
Estrogens and medroxyprogesterone
Estrogens and methyltestosterone
Estrone
Ethinyl Estradiol
Ethinyl Estradiol and ethynodiol diacetate
Ethinyl Estradiol and levonorgestrel
Ethinyl Estradiol and norethindrone

Ethinyl Estradiol and norgestrel
Mestranol and norethindrone
Polyestradiol

Rifamycins

Rifampin (Rifadin®)
Rifabutin (Mycobutin®)

Selective serotonin reuptake inhibitors (SSRI's)

Citalopram (Celexa)
Fluoxetine (Prozac)
Fluvoxamine (Luvox)
Paroxetine (Paxil)
Sertraline (Zoloft)

Sulfonamides

Sulfadiazine
Sulfisoxazole
Sulfamethoxazole (Gantanol®)

Tricyclic antidepressants

Amitriptyline (Elavil)
Amoxapine (Asendin)
Clomipramine (Anafranil)
Desipramine (Norpramin)
Doxepin (Sinequan)
Imipramine (Tofranil)
Nortriptyline (Pamelor , Aventyl)
Protriptyline (Vivactil)
Trimipramine (Surmontil)

Appendix A. Summary of Published Comparative or Placebo Controlled Clinical Trials for Anticonvulsants in Neuropathic Pain				
Reference	Study Design	Population	Dose regimens	Primary Outcome Result
Diabetic Peripheral Neuropathy (DPN)				
Richter et al, 2005 ²¹⁴	Experimental: randomized, double-blind, placebo-controlled Treatment duration: 6 weeks	246 patients ≥ 18 years with a 1-5 year history of DPN, pain score ≥ 40mm on the SF-MPQ (VAS 0-100 mm), and average daily pain score ≥ 4 (scale 0-10) Patients previously exposed to gabapentin were allowed in study.	Pregabalin 150 mg/day (n = 79) Pregabalin 600 mg/day (n = 82) Placebo (n = 85) Medication given in divided doses three times daily	Pregabalin 600 mg/d > Placebo Pregabalin 150 mg/d = Placebo <u>Primary outcome</u> Mean Pain Score (scored 0 – 10) Pregabalin 600 mg: 4.3 Placebo: 5.6, p = 0.0002 Responders (≥ 50% decrease in baseline pain score at endpoint, % of patients) Pregabalin 600 mg: 39%, Placebo: 15%, p = 0.002 vs placebo
Rosenstock et al, 2004 ²¹⁵	Experimental: randomized, double-blind, placebo-controlled Treatment duration: 8 weeks	146 patients ≥ 18 years with a 1-5 year history of DPN, pain score ≥ 40mm on the SF-MPQ (VAS 0-100 mm), and average daily pain score ≥ 4 (scale 0-10). Patients were excluded if they had failed gabapentin ≥ 1200 mg/day.	Pregabalin 300 mg/day (n = 76) Placebo (n = 70) Medication given in divided doses three times daily	Pregabalin > Placebo <u>Primary outcome</u> Mean Pain Score (scored 0 – 10) Pregabalin: 4.0 Placebo: 5.3, p < 0.0001 Responders (≥ 50% decrease in baseline pain score at endpoint, % of patients) Pregabalin: 40%, Placebo: 14.5%, p = 0.001

Appendix A. Summary of Published Comparative or Placebo Controlled Clinical Trials for Anticonvulsants in Neuropathic Pain				
Reference	Study Design	Population	Dose regimens	Primary Outcome Result
Lesser et al, 2004 ²¹⁶	Experimental: randomized, double-blind, placebo-controlled Treatment duration: 5 weeks	338 patients ≥ 18 years with a 1-5 year history of DPN, pain score ≥ 40mm on the SF-MPQ (VAS 0-100 mm), and average daily pain score ≥ 4 (scale 0-10). Patients were excluded if they had failed gabapentin ≥ 1200 mg/day.	Pregabalin 75 mg/day (n = 77) Pregabalin 300 mg/day (n = 81) Pregabalin 600 mg/day (n = 82) Placebo (n = 97) Medication given in divided doses three times daily	Pregabalin > Placebo <u>Primary outcome</u> Mean Pain Score (score 0 – 10) Pregabalin 300 mg: 3.8 Pregabalin 600 mg: 3.6 Placebo: 5.1, p = 0.0001 vs placebo for both doses Responders (% of patients with ≥ 50% decrease in baseline pain score at endpoint) Pregabalin 300 mg 46% Pregabalin 600 mg 48% Placebo: 18%
Freynhagen et al ²¹⁷	Experimental: randomized, double-blind, placebo-controlled Treatment duration: 12 weeks	338 patients ≥ 18 years with painful DPN ≥ 6 months or PHN ≥ 3 months after healing of herpes zoster skin rash, pain score ≥ 40 mm on the SF-MPQ (VAS 0-100 mm) Patients previously exposed to gabapentin were allowed in study.	Pregabalin 150 – 600 mg/day flexible dosing (n=141) Pregabalin 600 mg/day (n=132) Placebo (n=65) Medication given in divided doses twice daily.	Pregabalin > Placebo <u>Primary outcome</u> Responders (% of patients with > 50% decrease in baseline pain score at endpoint) Pregabalin flex dose: 48.2% Pregabalin fixed dose: 52.3% Placebo: 24% (p<0.001 for each pregabalin group vs placebo).
Backonja et al ³⁰	Experimental: randomized, double-blind, placebo-controlled Treatment duration: 8 weeks	165 patients ≥ 18 years with a 1-5 year history of DPN, pain score ≥ 40mm on the SF-MPQ (VAS 0-100 mm), and average daily pain score ≥ 4 (scale 0-10)	Gabapentin (week 1: 900 mg/d, week 2: 1800 mg/d, week 3: 2400 mg/d, week 4: 3600 mg/day. Patients continued on their maximal tolerated dose for an additional 4 weeks).(n=84) Placebo (n=81)	<u>Primary outcome</u> Mean Pain Score (score 0 – 10) Gabapentin: 3.9 Placebo: 5.1, p < 0.001 Change in pain score from baseline Gabapentin -2.5 Placebo -1.4 Data for responders with > 50% decrease from baseline in pain scores were not presented.

Appendix A. Summary of Published Comparative or Placebo Controlled Clinical Trials for Anticonvulsants in Neuropathic Pain				
Reference	Study Design	Population	Dose regimens	Primary Outcome Result
Simpson ⁴³	Experimental: randomized, double-blind, placebo-controlled study. Treatment duration: 8 weeks for each study part.	60 patients with DPN > 3 months, pain score \geq 40mm on the SF-MPQ (VAS 0-100 mm), and average daily pain score \geq 4 (scale 0-10)	<p><u>Part 1 of study</u> Gabapentin dose titrated up to 3600 mg/day over 4 weeks then maintained for 4 more weeks (n=30) Placebo (n=30)</p> <p><u>Part 2 of study</u> <i>Patients who had no or minimal improvement from part 1 of study</i> Gabapentin (maximum tolerated dose (MTD) from part 1 of study) + Venlafaxine 75 mg twice daily (n=6) Or Gabapentin (MTD from part 1 of study) + placebo (n=5)</p>	<p>Gabapentin > placebo Gabapentin + venlafaxine > gabapentin (for gabapentin nonresponders).</p> <p><u>Primary Outcome</u> Part 1 Mean change in pain score from baseline: Gabapentin: -2.4 Placebo: -0.5, p<0.01. 12 patients in gabapentin group had no improvement or worsened compared with 20 patients in placebo group.</p> <p>Part 2 Mean change in pain score from baseline: Gabapentin + venlafaxine: -2.0 Gabapentin + placebo: -0.5, p<0.01.</p>

Appendix A. Summary of Published Comparative or Placebo Controlled Clinical Trials for Anticonvulsants in Neuropathic Pain				
Reference	Study Design	Population	Dose regimens	Primary Outcome Result
Gilron et al ⁴²	<p>Experimental: randomized, double-blind, active-control, cross-over study.</p> <p>Treatment duration: 5 weeks for each study part (total duration 20 weeks).</p>	57 patients > 18 years with either DPN (n=35) or Post herpetic neuralgia (n=22) who had moderate pain for > 3 months.	<p>Morphine 120 mg/day</p> <p>Gabapentin 3200 mg/day</p> <p>Morphine 60 mg/day + gabapentin 2400 mg/day</p> <p>Active control (lorazepam 1.6 mg/day)</p>	<p>Gabapentin + morphine > gabapentin = morphine > placebo</p> <p><u>Primary Outcome</u> Mean pain intensity (0-10 scale) Baseline: 5.72 ± 0.23 Placebo: 4.49 ± 0.34 Gabapentin: 4.15 ± 0.33 Morphine 3.70 ± 0.34 Gabapentin + morphine: 3.06 ± 0.33, (p=0.04 morphine alone, p<0.001 gabapentin alone, or p<0.001 placebo).</p> <p><u>Secondary Outcomes</u> Maximal tolerated doses: Morphine 45.3 mg Gabapentin 2207 mg Morphine 34.4 mg + gabapentin 1705 mg Lorazepam 1.38 mg</p> <p>Percent of patients completing study and reporting moderate pain relief: Placebo: 31% Morphine: 80% Gabapentin: 61% Morphine + gabapentin: 78%. P< 0.05 for all groups vs placebo.</p>

Appendix A. Summary of Published Comparative or Placebo Controlled Clinical Trials for Anticonvulsants in Neuropathic Pain				
Reference	Study Design	Population	Dose regimens	Primary Outcome Result
Gorson et al ⁴⁰	Experimental: randomized, double-blind, placebo-controlled, cross-over study. Treatment duration 6 weeks with a 3 week washout (total study duration 15 weeks) Note: washout period in this study was inadequate as pain scores did not return to baseline in patients who first gabapentin in the first phase.	40 patients with DPN for > 3 months who had pain that interfered with daily activity or sleep	Gabapentin 900 mg/day (n=19) Placebo (n= 21)	Gabapentin = placebo <u>Primary Outcome</u> Present pain intensity (0-10 scale) Gabapentin 1.2 Placebo 0.3 (p=0.2) Visual Analog Scale (0-10 mm) Gabapentin 1.8 Placebo 1.4 (p=0.42) McGill pain questionnaire: Gabapentin 8.9 Placebo 2.2 (p=0.03)
Morello et al ³²	Experimental: randomized, double-blind, cross-over study Treatment duration: 6 weeks with 1 week washout period (total study duration 13 weeks)	28 patients > 18 years with DPN for > 3 months, and CrCl \geq 30 mL/min.	Gabapentin 900 – 1800 mg/day Amitriptyline 25 – 75 mg/day	Gabapentin = amitriptyline <u>Primary Outcome</u> Mean change in pain score from baseline: Gabapentin: 0.31 \pm 0.064 Amitriptyline 0.44 \pm 0.089, p=NS. % of patients reporting complete, a lot, or moderate pain relief: Gabapentin: 52% Amitriptyline: 67%, p=NS.
Dalocchio et al ⁴¹	Experimental: open label, randomized, parallel group study. Treatment duration: 12 weeks	25 patients > 60 yrs with DPN	Gabapentin 1200 – 2400 mg/day titrated to maximum tolerated dose.(n=13) Amitriptyline 30 – 90 mg/day titrated to maximum tolerated dose.(n=12)	Gabapentin > amitriptyline <u>Primary Outcome</u> Pain intensity score (0-4 pt scale) Change from baseline: Gabapentin: -1.9 Amitriptyline: -1.3, p=0.02

Appendix A. Summary of Published Comparative or Placebo Controlled Clinical Trials for Anticonvulsants in Neuropathic Pain				
Reference	Study Design	Population	Dose regimens	Primary Outcome Result
Gomez-Perez et al ⁶³	Experimental: randomized, double-blind, cross-over study Treatment duration 4 weeks with 2-4 week washout period (total study duration 10-12 weeks)	16 patients > 18 years with diabetes and DPN > 6 months.	Carbamazepine 300 mg x 15 days then 600 mg x 15 days. Nortriptyline 30 mg/ fluphenazine 1.5 mg x 15 days then dose doubled.	Carbamazepine = nortriptyline/fluphenazine. <u>Primary Outcome</u> Mean percent change in pain at 30 days: Carbamazepine: 49% Nortriptyline/fluphenazine: 66%, p=NS
Rull et al ⁶¹	Experimental: randomized, double-blind, cross-over study Treatment duration: 6 weeks (3 treatments each 2 weeks) Study had inadequate washout period.	30 patients > 18 years with diabetes > 3 years and DPN	Group A: Carbamazepine 600 mg x 2 weeks then placebo for 2 weeks then carbamazepine 600 mg for 2 weeks (n=14) Group B: Placebo for 2 weeks then carbamazepine 600 mg for 2 weeks then placebo for 2 weeks.(n=16)	Results not clearly summarized. No statistics performed. Efficacy based on subjective descriptive evaluations. No reliable conclusions about the efficacy of carbamazepine can be made.
Dogra et al ²¹⁸	Experimental: randomized, double-blind, placebo-controlled study. Treatment duration: 16 weeks.	146 patients with > 6 months history of DPN, and pain score \geq 50mm on VAS (0-100 mm)	Oxcarbazepine titrated to 1800 mg/day (n=69) Placebo (n=77)	Oxcarbazepine > placebo <u>Primary Outcome</u> Average change in VAS score from baseline Oxcarbazepine: -23.4 Placebo: -14.7, p=0.01. Percent of patients with a > 50% reduction in VAS from baseline Oxcarbazepine: 35.2% Placebo:18.4%, p=0.01.
Kochar et al ¹³²	Experimental: randomized, double-blind, placebo-controlled cross-over study. Randomization not described. Treatment duration:4 weeks each (total duration 8 weeks). No washout period defined.	48 patients ages 44-73 years with diabetes \geq 2 years who have DPN (duration not defined)	Valproic acid 1200 mg/day (n=24) Placebo (n=24)	Valproic acid > placebo Primary efficacy outcomes not defined. Mean change in McGill Pain score from baseline to week 4: Valproic acid 3.41 Placebo 4.6 (p=0.028).

Appendix A. Summary of Published Comparative or Placebo Controlled Clinical Trials for Anticonvulsants in Neuropathic Pain				
Reference	Study Design	Population	Dose regimens	Primary Outcome Result
Otto et al ²¹⁹	Experimental: randomized, double-blind, placebo-controlled cross-over study. Treatment duration: 4 weeks each (total duration 8 weeks). No washout period defined.	34 patients > 20 years with polyneuropathy \geq 6 months.	Valproic Acid 1500 mg/day Placebo	Valproic acid = placebo No differences in pain rating scales were observed between treatments. Total pain rating (0-10 scale) Baseline: 6 Valproic acid: 5 Placebo: 6, p=0.24
Atli et al ¹⁴³	Experimental: randomized, double-blind, placebo-controlled study Treatment duration: 12 weeks	42 patients \geq 18 years with a \geq 3 month history of DPN, pain score \geq 40mm on the SF-MPQ (VAS 0-100 mm), and/or average daily pain score \geq 4 (scale 0-10)	Zonisamide 300 – 600 mg/day (n=13) Placebo (n=12)	Zonisamide = placebo <u>Primary Outcome</u> Mean change in VAS score Zonisamide: -17.7 Placebo: -6.9, p=0.15.
Eisenberg ⁴⁵	Experimental: randomized, double-blind study Treatment duration: 8 weeks	59 patients \geq 18 years with a >6 months pain from DPN, and average daily pain score \geq 4 (scale 0-10)	Lamotrigine 400 mg/day (titrated up from 25 mg) (n=27) Placebo (n=26)	Lamotrigine 200 – 400 mg > placebo <u>Primary Outcome</u> Mean change in pain score from baseline: Lamotrigine: 2.2 ± 0.1 Placebo 1.2 ± 0.1 , p<0.001 for lamotrigine doses 200, 300 and 400 mg. 50% reduction in pain (observed weeks 5-8): Lamotrigine 44% Placebo 19% Nonresponders: Lamotrigine 27% Placebo 58%

Appendix A. Summary of Published Comparative or Placebo Controlled Clinical Trials for Anticonvulsants in Neuropathic Pain				
Reference	Study Design	Population	Dose regimens	Primary Outcome Result
Saudek et al ⁴⁷	Experimental: randomized, double-blind, cross-over study Treatment duration: 23 weeks on phenytoin and 23 weeks on placebo.	12 patients ages 30-75 with > 1 year history of diabetes. Duration and quality of DPN not defined	Phenytoin –dose titrated to serum level between 5 and 20 mg/L.(n=12) Placebo (n=12)	Phenytoin = placebo Phenytoin may alter blood glucose control- not optimal for diabetic patients. No difference in symptoms between placebo and phenytoin.
Chadda and Mathur ⁴⁶	Experimental: double-blind, placebo controlled, cross-over study. Randomization method not defined. Treatment duration: 2 weeks with 1 week washout period (total duration 5 weeks)	40 patients > 18 years old with diabetes > 3 months who had DPN.	Phenytoin 100 mg TID Placebo	Phenytoin > placebo <u>Primary Outcome</u> Pain score ≥ 4 (marked improvement): Phenytoin 73% Placebo 15% Pain assessed on 6 point (0-5) Likert scale. No statistical analysis performed. Study duration too short Evaluation of pain not well-defined and subjective.
Thienel et al ⁴⁴	Pooled analysis of three identical randomized, double-blind, placebo controlled trials. Treatment duration 18-22 weeks	1269 patients > 18 years with diabetes and peripheral polyneuropathy ≥ 6 months	Topiramate 100 mg/day (n=253) 200 mg/day (n=372) 400 mg/day (n=260) Placebo (n=384) Short-acting analgesics allowed.	Topiramate = placebo <u>Primary Outcome</u> Pain intensity score (VAS 100 mm), change from baseline: No differences were observed between any of the groups. 18% of patients had baseline VAS scores < 40 mm, indicating more mild pain
Raskin et al ³⁶	Experimental: randomized, double-blind, placebo-controlled study. Study duration: 12 weeks.	323 patients > 18 years with PDN ≥ 3 months and VAS score ≥ 40 mm.	Topiramate 400 mg/day (n=214) Placebo (n=109) Short-acting analgesics allowed for first 6 weeks only.	Topiramate > placebo <u>Primary Outcome</u> Pain intensity score (VAS 100 mm), change from baseline: Topiramate -21.8 Placebo -15.1, p=0.038. 50% decrease in VAS score from baseline: Topiramate 35.6% Placebo 21.1%, p=0.005.

Appendix A. Summary of Published Comparative or Placebo Controlled Clinical Trials for Anticonvulsants in Neuropathic Pain				
Reference	Study Design	Population	Dose regimens	Primary Outcome Result
Postherpetic Neuralgia				
Dworkin et al ⁵¹	Experimental: randomized, double-blind, placebo-controlled Treatment duration: 8 weeks	173 patients ≥ 18 years with pain for ≥ 3 months after healing of herpes zoster skin rash, pain score ≥ 40 mm on the SF-MPQ (VAS 0-100 mm), and an average daily pain score ≥ 4 (scale 0-10). Patients were excluded if they had failed gabapentin ≥ 1200 mg/day.	Pregabalin 300 – 600 mg/day (n=89), dose based on renal function Placebo (n=84) Medication given in divided doses three times daily Concomitant medications included antidepressants, NSAIDs and aspirin.	Pregabalin > placebo <u>Primary outcome</u> Mean Pain Score (scored 0 – 10) Pregabalin: 3.6 Placebo: 5.29, p = 0.0001 Responders (% of patients with a ≥ 50% decrease in baseline pain score at endpoint) Pregabalin: 50% Placebo: 20%, p< 0.05
Sabatowski et al ⁵²	Experimental: randomized, double-blind, placebo-controlled Treatment duration: 8 weeks	238 patients ≥ 18 years with pain for > 6 months after healing of herpes zoster skin rash, pain score ≥ 40 mm on the SF-MPQ (VAS 0-100 mm), and an average daily pain score ≥ 4 (scale 0-10). Patients were excluded if they had failed gabapentin ≥ 1200 mg/day.	Pregabalin 150 mg/day (n = 81) Pregabalin 300 mg/day (n = 76) Placebo (n = 81) Medication given in divided doses three times daily. Concomitant medications included antidepressants, NSAIDs and aspirin.	Pregabalin 300 mg/d > Placebo Pregabalin 150 mg/d ≥ Placebo <u>Primary outcome</u> Mean Pain Score (scored 0 – 10) Pregabalin 150 mg: 5.14, p = 0.0002 vs placebo Pregabalin 300 mg: 4.76, p = 0.0001 vs placebo Placebo: 6.33 Responders (% of patients with a ≥ 50% decrease in baseline pain score at endpoint) Pregabalin 150 mg: 26%, p = 0.006 Pregabalin 300 mg: 28%, p = 0.003 Placebo: 10%

Appendix A. Summary of Published Comparative or Placebo Controlled Clinical Trials for Anticonvulsants in Neuropathic Pain				
Reference	Study Design	Population	Dose regimens	Primary Outcome Result
Rowbotham et al ²⁹	Experimental: randomized, double-blind, placebo-controlled trial Study duration: 8 weeks	229 patients ≥ 18 years with pain for > 3 months after healing of herpes zoster skin rash, pain score ≥ 40 mm on the SF-MPQ (VAS 0-100 mm), and an average daily pain score ≥ 4 (scale 0-10).	Gabapentin titrated up to 3600 mg/day or maximum tolerated dose (n=109) Placebo Concomitant medications included antidepressants and narcotics.	Gabapentin > placebo <u>Primary outcome:</u> Daily pain score (0-10) Mean change from baseline: Gabapentin: -2.1 (33% reduction) Placebo: -0.5 (7.7% reduction), p<0.01. Mean pain score: Gabapentin: 4.2 Placebo: 6
Rice et al ²⁸	Experimental: randomized, double-blind, placebo-controlled trial Study duration: 7 weeks	334 patients ≥ 18 years with pain for > 3 months after healing of herpes zoster skin rash and an average daily pain score ≥ 4 (scale 0-10).	Gabapentin 1800 mg/day (n=115) Gabapentin 2400 mg/day (n=108) Placebo (n=111) Doses were titrated over a 16-day period. Concomitant medications included antidepressants, codeine and acetaminophen..	Gabapentin 1800 mg = gabapentin 2400 mg > placebo <u>Primary Outcome</u> Daily pain score (0-10) Change in score from baseline to study endpoint: Placebo: -1.1 (15.7%) Gabapentin 1800 mg: -2.2 (34.5%) Gabapentin 2400 mg: -2.3 (34.4%), p<0.01 for both gabapentin groups vs placebo. Responders (% of patients with a ≥ 50% decrease in baseline pain score at endpoint) Gabapentin 1800 mg: 32% Gabapentin 2400 mg: 34% Placebo: 14%, p<0.01 for both gabapentin groups vs placebo.

Abbreviations: SF-MPQ = Short form McGill Pain Questionnaire, VAS = Visual Analog Scale